

A Two-week Interval Is Better Than a Three-week Interval for Reducing the Recurrence Rate of Hand-foot Viral Warts after Cryotherapy: A Retrospective Review of 560 Hand-foot Viral Warts Patients

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Background: Viral warts are a common infectious disease and liquid nitrogen cryotherapy is one of the most common methods for treatment of these warts. Hand-foot viral warts frequently recur and reduce quality of life as well. **Objective:** To find the ideal treatment interval between cryotherapy sessions that can influence not only the cure rate but also the recurrence rate for hand-foot viral warts. **Methods:** A retrospective study was designed to compare a 2 week interval and a 3 week interval between cryotherapy sessions on hand-foot viral warts with respect to cure rate, recurrence rate, treatment number, duration of treatment, mean time to recurrence and adverse events. **Results:** A total of 560 patients were enrolled. The overall cure rate was 75.7% and the recurrence rate was 19.6%. The mean time to recurrence was 7.8 months (range 1 ~ 26 months). For the 2-week and 3-week groups, cure rates were, respectively, 76.6% (196) and 75.0% (228); recurrence rates were 13.3% (26) and 25.0% (57). The mean time to recurrence was 9.8 months and 6.9 months, respectively. Adverse events were not statistically different. **Conclusion:** We suggested that 2-week cryotherapy is optimal not only because of the rapid cure but also because of the lower recurrence rate and similar adverse events. (*Ann Dermatol* 23(1) 53 ~ 60, 2011)

-Keywords-

Cryotherapy, Recurrence rate, Treatment interval, Verruca,

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Wart

INTRODUCTION

Warts, the cutaneous infection by DNA containing the human papilloma virus (HPV), are commonly diagnosed in dermatology clinics¹. Common warts represent about 70% of cutaneous warts and usually develop on the hands and feet in children, whereas plantar and flat warts occur in a slightly older population¹. Although the warts showed spontaneous clearance after two years without treatment in 40% of children², warts typically continue to increase in size and distribution and may become more resistant to therapy. Today, there are plenty of therapeutic modalities that are used to treat warts, but there is no single therapy that is 100% effective³. Among these modalities, cryotherapy is the preferred method due to safety, convenience of application, and lack of need for anesthesia^{1,4}. Hand-foot viral warts cause inconveniences in our daily lives due to the anatomical location; and successful treatment will improve the quality of life of the patient. So, factors such as treatment intervals, which affect the results of wart treatment, is important. Although there are many reports considering the cure rate of cryotherapy, there are no reports studying the relationship between recurrence rate and the treatment interval of cryotherapy.

We conducted this study, therefore, to determine the ideal treatment interval of cryotherapy, which could affect not only the cure rate but also the recurrence rate of hand-foot viral warts treated by cryotherapy.

MATERIALS AND METHODS

Patients

This was a retrospective study of 560 cases of hand-foot viral warts treated by cryotherapy primarily at our clinic in the Hallym University Sacred Heart Hospital between January 2006 and June 2008 and fully followed up. We reviewed the medical records in June 2009 to make the minimal follow up duration 12 months. Patients who received cryotherapy only once were excluded regardless of results. We also excluded (1) patients who were taking an immunosuppressor, (2) those that were managed by combination therapy, (3) those that had irregular therapy due to the patient's non-cooperation, (4) those were out of contact, and (5) those who showed natural regression after several treatments. Hand-foot viral warts included common warts, plantar warts and periungual warts on the hands (distal from the wrist) and feet (distal from the ankle).

Treatment

In our clinic, cryotherapy was performed with a spraygun (CRY-AC-3, Brymill Cryogenic system) or cotton wool bud method for the triple-long freeze technique (3 cycles of 10 seconds sustained freeze and thaw). Before cryotherapy, mild paring was routinely performed, with care taken to avoid any bleeding. Patients were randomly assigned to 2-week or 3-week treatment intervals.

Assessment

Patients were divided into the following groups based on the location of the wart: hand only, foot only, and both hands and feet. We defined "cured patients" as those whose warts were cured based on an examination made at their last follow-up visit, and noted in their medical records. If the patient did not come for a follow-up visit, we telephoned the patient two or three weeks after the last treatment, and asked whether or not their warts had cleared. "failed patients" were separate from "cured patients". They included patients who wanted to stop cryotherapy or to change to other treatment methods due to pain or lack of improvement. "recurred patients" were defined as patients who returned with the same skin lesions after their medical records had indicated that their warts had been cured. If the patient returned with the same symptoms after longer than two months without cured decision, we asked them, either in person or by telephone call, to identify if the verruca recurred or the patient showed poor compliance. We recorded any post-treatment adverse ongoing symptoms such as blistering, pain, or erosion, but only if the patient complained of the symptom at their follow-up visit.

Finally, we reviewed the charts retrospectively to determine the post-cryotherapeutic cure rate and recurrence rate of hand and foot viral warts, with regard to different treatment intervals. Additionally, the number of treatments, treatment duration until cure, mean time to recurrence, and adverse events due to treatment were evaluated.

Statistical analysis

Pearson's chi-square tests were used to evaluate the difference in the cure rate and the recurrence rate between the two treatment interval subgroups. Student's t-test was used to compare the 'mean treatment number until cure', 'mean duration until cure', 'mean time to recurrence' and adverse events of treatment. For statistical analyses, we used SPSS version 12.0 (SPSS Inc., Chicago, IL, USA); *p*-values <0.05 were considered to be significant.

RESULTS

Demographic data

Five hundred and sixty hand-foot viral warts patients (310 males and 250 females) were included in this study. The mean age of the patients was 20.1 ± 11.5 . Of the 560 patients, 282 (50.4%) had warts only on their feet, 199 patients (35.5%) had warts only on their hands, and 79 patients (14.1%) had warts on both their hands and their feet (Table 1, Fig. 1). Of the 560 study participants, 83.6% were 20 years old or less.

Of the 560 participating patients, 256 patients (145 males and 111 females) were treated using two-week intervals and 304 patients (165 males and 139 females) were

Table 1. Characteristics and distribution of all patients enrolled in this study

Demographic data	Treatment interval, No. (%)		
	Total	2 weeks	3 weeks
Sex			
Male	310 (55.4)	145 (56.6)	165 (54.3)
Female	250 (44.6)	111 (43.4)	139 (45.7)
Age (yr)			
Mean \pm SD	20.1 ± 11.5	19.7 ± 10.5	20.5 ± 12.2
≤ 10	95 (17.0)	40 (15.6)	55 (18.1)
11 ~ 20	257 (45.9)	124 (48.4)	133 (43.8)
21 ~ 30	116 (20.7)	56 (21.9)	60 (19.7)
31 ~ 40	63 (11.3)	23 (9.0)	40 (13.2)
≥ 41	29 (5.1)	13 (5.1)	16 (5.2)
Subtype			
Foot only	282 (50.4)	129 (50.4)	153 (50.3)
Hand only	199 (35.5)	90 (35.2)	109 (35.9)
Hands and feet	79 (14.1)	38 (14.4)	41 (13.8)
Total patients	560 (100)	256 (100)	304 (100)

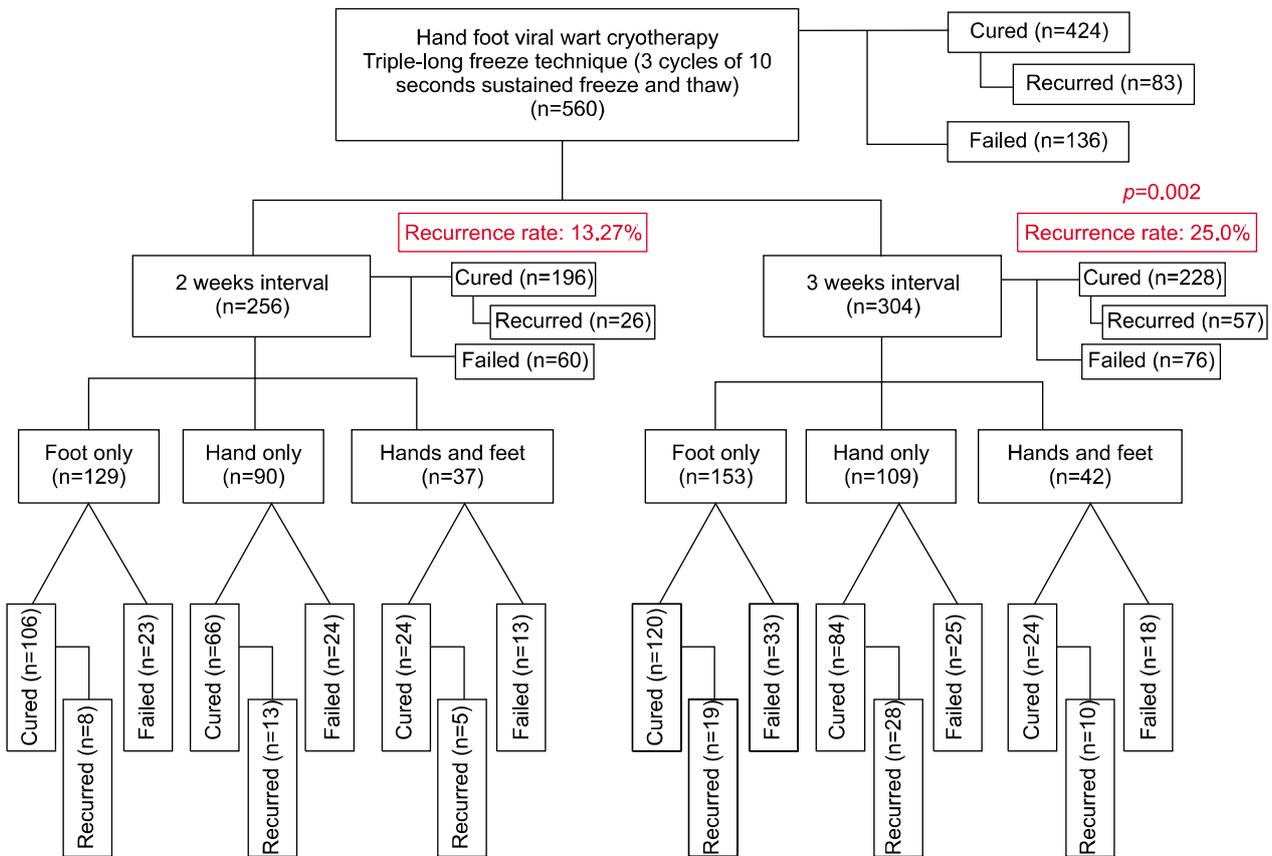


Fig. 1. Study design with a retrospective review.

Table 2. Cure rate and recurrence rate of total enrolled patients

Characteristics	Treatment interval, No. (%)			p-value
	Total	2 weeks	3 weeks	
Total patients	560 (100)	256 (100)	304 (100)	
All subtypes (foot only+hand only+hands and feet)				
Cured patients (cure rate)	424 (75.7)	196 (76.6)	228 (75.0)	0.397
Failed patients (failure rate)	136 (24.3)	60 (23.4)	76 (25.0)	—
Recurred patients (recurrence rate)	83 (19.6*)	26 (13.3)	57 (25.0)	0.002 [†]
Mean treatment number until cure	3.37	3.20	3.51	0.117
Mean duration until cure (wk)	8.54	6.40	10.53	0.0001 [†]
Mean time to recurrence (mo)	7.8	9.79	6.89	0.046 [†]

*Recurrence rate=recurred patients number/cured patients number×100 (%) (Total recurrence rate=83/424×100=19.6%), [†]Statistically significant with p-values <0.05.

treated using three-week intervals. Age and subtype distributions for these two groups were similar to each other and to those of the total group (Table 1).

Response rate

As shown in Table 2, of the 560 treated patients, 424 (75.7%) were cleared of their warts; the treatment failed to work for 136 (24.3%). Furthermore, 83 patients (19.6%) experienced a recurrence of their warts. The 'mean time

to recurrence' was 7.8 months (range 1~26 months). Between the 2-week and 3-week interval groups, the cure rate was similar but the recurrence rates differed; they were 13.3% and 25.0%, respectively and this difference was statistically significant ($p=0.002$). 'Mean treatment number until cure' was similar between the two groups. The 2-week interval groups showed lower 'mean duration until cure' and longer 'mean time to recurrence', and it was statistically significant.

As shown in Table 3, the cure rate for each subtype was foot-only warts (80.1%), hand-only warts (75.4%), and warts on both hands and feet (60.8%). The recurrence rates for foot-only warts, hand-only warts, and warts on both hands and feet were 12.0%, 27.3% and 31.3%, respectively. Between 2-week and 3-week interval groups, recurrence rates showed statistically significant differences for the foot only and hand only subtypes ($p=0.042$ and $p=0.046$ respectively). Differences in 'mean duration until cure' were statistically significance in all subtypes. Only in the hand only subtype did 'mean time to recurrence' show a significantly longer time for the 2-week group ($p=0.039$).

Differences in results for the different age groups were not significant, except for the 'mean duration until cure' of

whole subgroups and the recurrence rate of the 11~20 age group (13.5% vs. 27.3%, $p=0.014$), the largest subgroup. But in the clinic, the recurrence rate and 'mean treatment number until cure' of the 2-week interval group were shorter and the mean time to recurrence was longer than for the 3-week interval group (data not shown). The cure rate for under 10 years-old, 11~20, 21~30, 31~40 and over 41 years-old subgroups were 90.5%, 75.9%, 69.8%, 68.3% and 65.5%, respectively. The recurrence rate for under 10 years-old, 11~20, 21~30, 31~40 and over 41 years-old subgroup were 18.6%, 20.5%, 18.5%, 20.9% and 15.8%, respectively.

Adverse events

As shown in Table 4, of the 560 treated patients, 86

Table 3. Cure rate and recurrence rate by subtypes

Characteristics	Treatment interval, No. (%)			p-value
	Total	2 weeks	3 weeks	
Foot only				
Cured patients (cure rate)	226 (80.1)	106 (82.2)	120 (78.4)	0.264
Failed patients (failure rate)	56 (19.9)	23 (17.8)	33 (21.6)	—
Recurred patients (recurrence rate)	27 (12.0)	8 (7.6)	19 (15.8)	0.042*
Mean treatment number until cure	3.6	3.4	3.8	0.315
Mean duration until cure (wk)	9.1	6.8	11.4	0.0001*
Mean time to recurrence (mo)	8.5	9.4	8.1	0.639
Hand only				
Cured patients (cure rate)	150 (75.4)	66 (73.3)	84 (77.1)	0.328
Failed patients (failure rate)	49 (24.6)	24 (26.7)	25 (22.9)	—
Recurred patients (recurrence rate)	41 (27.3)	13 (19.7)	28 (33.3)	0.046*
Mean treatment number until cure	2.9	2.8	3.0	0.751
Mean duration until cure (wk)	7.5	5.6	9.1	0.0001*
Mean time to recurrence (mo)	8.1	11.3	6.7	0.039*
Hands and feet				
Cured patients (cure rate)	48 (60.8)	24 (64.9)	24 (57.1)	0.367
Failed patients (failure rate)	31 (39.2)	13 (35.1)	18 (42.9)	—
Recurred patients (recurrence rate)	15 (31.3)	5 (20.8)	10 (41.7)	0.106
Mean treatment number until cure	3.6	3.5	3.8	0.471
Mean duration until cure (wk)	9.0	6.9	11.3	0.048*
Mean time to recurrence (mo)	5.6	6.5	5.2	0.572

*Statistically significant with p -values <0.05 .

Table 4. Adverse events by treatment intervals

Complications	Treatment interval, No. (%)			p-value
	Total	2 weeks	3 weeks	
Blistering	55 (9.8)	35 (13.7)	20 (6.6)	0.005*
Pain	14 (2.5)	7 (2.7)	7 (2.3)	0.655
Erosion	14 (2.5)	5 (2.0)	9 (3.0)	0.764
Hemorrhage	1 (0.2)	0	1 (0.3)	0.318
Edema	1 (0.2)	0	1 (0.3)	0.318
None	474 (84.6)	208 (81.2)	266 (87.5)	—
Total number of adverse events	86 (15.4)	47 (18.8)	38 (12.5)	0.276

*Statistically significant with p -values <0.05 .

(15.6%) complained about complications such as blistering (55, 9.8%), pain (14, 2.5%), erosion (15, 2.7%), hemorrhage (1, 0.2%), and edema (1, 0.2%). Clinically, the group that was treated using two-week intervals showed more complications, but this result was not significant ($p=0.276$). In the retrospective chart review, there were no adverse events that remained for more than 1 month after the last treatment.

DISCUSSION

Liquid nitrogen, with a vaporization temperature of -196°C , is the most frequently used cryogen¹. Clearing the wart may be accomplished through necrotic destruction of HPV-infected keratinocytes or by inducing local inflammation that triggers an effective cell-mediated immunity⁵. Both humoral and cellular immunity are important in the response to HPV infection by resistance to reinfection and wart regression respectively⁶. The mechanism of tissue destruction by cryotherapy is probably multi-factorial⁷. Ice formation in the cell is directly damaging to their membrane and intracellular structures. Cells are also damaged by osmotic gradient changes across their cell wall, as well as by vascular supply disruption⁷.

In the literature, there are two broad methods to divide

viral wart subtypes. One is dividing them as common warts, palmoplantar warts, and periungual warts. The other is dividing them by location as hand only, foot only, and both hands and feet⁸⁻¹². We grouped the subtype as hand only, foot only, and both hands and feet, because the first therapy for hand-foot warts is usually cryotherapy, and there is no overlap between subtypes.

There are many studies that compared the efficacy of cryotherapy with other modalities and assessed cure rates for cryotherapy of viral warts (Table 5)^{3,4,8-19}. These studies show cure rates ranging from 43% to 83%. In our study, the overall cure rate was 75.7%, and the cure rate for each subtype of feet only, hands only, and both hands and feet was 80.1%, 75.4%, and 60.8%, respectively (Tables 2, 3). Compared to other studies, our cure rates are relatively high. We surmised that the high efficacy may be due to our effective cryotherapy regimen. Before cryotherapy, we routinely pared the lesions. In addition, we usually performed 3 cycles of a longer freeze (sustained 10 s freeze)⁸ method at 2 or 3 week intervals. Another reason for the high efficacy could be the patients' age distribution. Many reports suggested that if the patients had few warts with a short duration, was young and immunocompetent, it was easier to manage^{1,6}. In our study, 45.9% of reviewed patients were teenagers and

Table 5. Literature reviews of cryotherapy for viral warts

Year	Author	No. of patients	Criteria*	Cure rate (%)	Recurrence rate (%)	Cryotherapy method (methods/range/cycle/interval)
2010	This study	797	2	78.3 (foot 81/hand 79/both 63)	20.19	Spray gun or CWB/10 seconds/triple freeze-thaw/2 or 3 wk
2009	Dhar et al. ⁴	34	—	76.5	23	Spray gun/until 1 mm margin of ice halo/double freeze-thaw/3 wk
2008	Banihashemi et al. ¹⁴	30	Hand	70	—	CWB/10~20 seconds/once/weekly
2008	Choi et al. ¹⁵	75	—	50.8	21.6	Spray gun/-/2 or 3 freeze-thaw/2 or 3 wk
2008	Canpolat et al. ¹⁸	20	—	65	—	Study/2 mm margin of ice halo/double freeze-thaw/3 wk
2007	Bohlooli et al. ¹⁷	14	—	56	35	-/-/once/1 and 2 weeks
2007	Adalatkhah et al. ¹³	44	Limbs	68.2	—	Spray gun/1 mm margin of ice halo/-/2 wk
2006	Kim et al. ¹²	180	2	44.2 (foot 58/hand 30.4/both 38.7)	16.7	Spray gun/2~4 mm margin of ice halo/2 or 3 freeze-thaw/2 or 3 wk
2004	Rivera and Tyring ³	Review	—	50~70	20~30	Review journal
2002	Focht et al. ¹⁶	25	—	60	—	-/10 seconds/single freeze-thaw method/2 or 3 wk
2001	Connolly et al. ⁸	100	2	64 (hand 68/foot 56)	—	Spray gun/study/once/2 wk
2001	Ahmed et al. ⁹	363	2	47 (hand 50/foot 41/both 29)	—	Study/2 mm margin of ice halo/double freeze-thaw/2 wk
1995	Bourke et al. ¹⁰	225	2	43	—	CWB/ice halo/once/study
1992	Berth-Jones and Hutchinson ¹¹	400	2	52 (3 mo) (foot 60/hand 54/both 25)	—	CWB/ice halo/once/3 wk
1990	Keefe and Dick ¹⁹	130	Hand	Early 83/late 57	—	CWB/ice halo/once/3 wk

CWB: cotton wool bud. *Criteria: 1=clinical subtype as common warts (*verruca vulgaris*), palmoplantar warts, and periungual warts. 2=clinical subtype by location as hand only, foot only, and both hands and feet.

83.6% were in their twenties or younger. This specific distribution of ages probably contributed to our high cure rate. We also found that the cure rate decreased as patients got older. Considering the subtype, and similar to other studies^{11,12}, the foot only group showed a higher cure rate than the others. We believe it was due to the high effectiveness of paring in the foot only group.

There are a few reports describing the recurrence rate after cryotherapy, and the results vary widely from 16.7% to 35%^{3,4,12,15,17}. In our study, the overall recurrence rate was 19.6%, and the recurrence rate of each subtype of foot only, hand only, and both hands and feet was 12%, 27.3%, and 31.3% respectively (Tables 2, 3). The recurrence rate in our study was similar to other studies. The exact etiology of recurrence is unknown, but some have suggested that it is caused by insufficient immunologic antiviral effects of cryotherapy for latent HPV infection, even though the infected tissues were removed by the procedure.

Although two-thirds of warts in children showed spontaneous regression when followed up for at least 2 years, viral warts can persist for years in many patients, representing a reservoir for HPV infection¹. Warts are spread by contact, either directly from person to person, or indirectly via fomites left on surfaces. Autoinoculation, therefore, can occur by scratching, shaving, or traumatizing the skin⁵. So, applying the keratolytics, a corrosive agent or some antiviral agent such as imiquimod, during the re-epithelization period after cryotherapy might be useful to prevent development of an HPV reservoir. And, it is important to teach the patients not to spread the virus themselves before or after cryotherapy. In our data, we found that disease recurrence occurred within 7.8 months (range 1~26 months). Because of this higher chance of recurrence within the 8 months after cryotherapy, we suggest that physicians who treat viral warts should remind patients to observe their lesions carefully at least for 8 months after the last cure decision.

The cure rate for the two-week interval treatment group and the three-week interval treatment group was similar. Considering the cure rate, our results were similar to those of Bunney et al.²⁰, which showed the cure rate for the two-week interval patients as 78% and the cure rate for the three-week interval patients as 75%. They suggest that the interval between treatments should not be longer than three weeks, because four weeks intervals showed a much lower cure rate of 40%. Furthermore, Bourke et al.¹⁰ suggest that the two-week interval is optimal because two-week interval treatment showed rapid cure after the same treatments numbers than three-week interval treatment and similar adverse events with the three-week

interval group. These previous studies did not discuss recurrence rates after cryotherapy. In our study, the overall recurrence rate for the 2-week interval treatment group was lower than that of the 3-week group and this difference was statistically significant (Table 2). Although each subgroup of the two-week interval group showed a lower recurrence rate clinically, the statistical significance was not shown for all subgroups (Table 3). As 'mean treatment number until cure' was similar between the two-week interval treatment group and the three-week interval treatment group, 'mean duration until cure' was lower for the two-week interval group and, thus, statistically significant. It indicated that the two-week interval cryotherapy showed a more rapid cure than the three-week interval treatment. Additionally, 'mean time to recurrence' for the two-week interval group was longer than for the three-week interval group, although it was statistically significant only in total group and hand only subtype patients.

We surmise the evidences of the priority for two week intervals in the cryotherapy of the hand-foot viral warts. Two week intervals will favor maintaining the immune response that occurs due to the keratolytic effects of cryotherapy. Among studies designed to find ideal modalities for treating viral warts, immune-associated methods evoke better cure results than cryotherapy^{4,13-15}. Additionally, imiquimod and diphenylcyclo-propenone immunotherapy showed quite a lower recurrence rate in the literature. They suggested that these modalities were able to prevent the recurrence of viral warts by maintaining the immune response^{3,21,22}. During normal wound healing, immune responses are activated by many cells such as T lymphocytes, macrophages and neutrophils and many cytokines and chemokines during the first week, the so called inflammation phase. After that, the wound healing process is skewed to restructuring to increase the strength of the wounded tissue²³. So, if cryotherapy is applied every two weeks, the immune response induction will be more frequent than using three week intervals; it also causes lower recurrence.

Every therapeutic modality has its adverse events. Cryotherapy to treat warts can result in various adverse events, including pain, erythema, discomfort and blistering during the procedure, pain, erythema, hemorrhagic blister formation and infection after the procedure and dyspigmentation and nail dystrophy after healing when treating periungual warts²⁴. We only evaluated post-treatment adverse events. In our study, 86 patients (15.6%) complained about post-treatment blistering, pain, erosion, hemorrhage and edema at their follow up visit (Table 4). Blistering was the most frequent complaint after cryo-

therapy, and no patients complained of serious side effects, such as frostbite or nerve injury. The group that received treatment at two-week intervals showed clinically more adverse events than the group that was treated at three-week intervals (48, 18.8% vs. 38, 12.5%, respectively). However, these results were not statistically significant. Only blistering showed a significant difference. One reason for this result could be that, with a three-week interval, doctors might easily overlook the adverse events because they had already healed and patients did not complain due to healing. Only blistering, which is relatively fast healing and reversible adverse events that do not impair long term quality of life were higher in the 2-week interval group. If the blistering is bothering the patients during the 2 weeks interval treatment, the doctor should inform the patient that the blistering will heal in several days and does not cause serious and permanent complications.

Being a retrospective study, this study has some limitations. First, the descriptions regarding the number, size and duration of viral warts were not considered because the data from the medical records were insufficient to analyze. This was due to the inconsistent way that medical records were made between dermatologists in our clinic. The evaluation of adverse events might be affected by this limitation also. Efficacy often varies widely and can differ by age, compliance, immunity, wart location, size, and duration. Second, a retrospective review has a selection bias. Grouping patients by clinical results and excluding "out of contact" patients could induce bias. We therefore tried to minimize bias by doing a triple review and data analysis by three reviewers. Additionally, if we divided the patients into clinical subtypes (common warts, palmoplantar warts and periungual warts), the results might be different. Fundamentally, a double-blind, randomized, controlled study is needed.

Based on our new evidence, we conclude that two-week interval cryotherapy is optimal, not only due to more rapid cure, as was suggested by a previous study, but also because of the considerably lower recurrence rate, the similar complication rate and longer 'mean time to recurrence' than the three-week interval cryotherapy. These new findings could improve convenience for patients with viral warts of the hands and feet by facilitating the patient's use of his or her hands and feet in daily life, by decreasing the number of clinic visits and, ultimately, increasing the quality of life during the treatment of hand-foot viral warts. Hence, we suggest that routine mild pairing followed by a triple-long freeze technique (3 cycles of 10 seconds sustained freeze and thaw) using two-week intervals between cryotherapy

sessions, is the optimal method for using cryotherapy for hand-foot viral warts.

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