

Evaluation of Factors That May Affect Success of Cryotherapy in the Treatment of Warts: A Retrospective Cross-Sectional Study

Siğil Tedavisinde Kriyoterapinin Başarısını Etkileyebilecek Faktörlerin Değerlendirilmesi: Retrospektif Kesitsel Bir Çalışma

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ABSTRACT Objective: Success of the treatment of warts with cryotherapy differs from patient to patient. We aimed to evaluate how the age and gender of the patient, the type, number, duration, localization of warts and cryotherapy session intervals affect the success of treatment. **Material and Methods:** After ethics committee approval had been received, the medical files of patients with diagnosis of wart, between June 2016 and June 2019, were analysed retrospectively. Demographic and clinical features of patients were recorded. Patients who did not improve clinically after 6 sessions were considered resistant to treatment. Demographic and clinical features were compared between treatment resistant and non-resistant groups by using SPSS 17 (Chicago, IL, USA), two-sided p value <0.05 was considered statistically significant. **Results:** Fifty-six of 98 patients (57.2%) were female and 42 of them (42.8%) were male. The mean age was 21.98±12.80 years. Among all patients, 28 (28.6%) of them were resistant to the therapy. In the resistant group, F/M ratio was 20/8 (71.4%/28.6%) and in the non-resistant group, 36/34 (51.4%/48.6%). The difference between groups was statistically significant (p=0.04). Patients with wart sizes of 0-4.9 mm, 5-10 mm, >10 mm were compared and resistance rates were found respectively 14.7%, 31.5%, 60%. Difference between subgroups was statistically significant (p=0.01). The mean age, lesion localization, lesion number, verruca subtype, duration of the disease and the session intervals for both groups were found similar (p>0.05). **Conclusion:** Treatment success was found to be lower in women and in patients with larger warts.

ÖZET Amaç: Kriyoterapi ile siğil tedavisinin başarısı hastadan hastaya farklılık göstermektedir. Hastanın yaşı ve cinsiyeti, siğillerin tipi, sayısı, süresi, lokalizasyonu ve kriyoterapi seans aralıklarının tedavi başarısını nasıl etkilediğini değerlendirmeyi amaçladık. **Gereç ve Yöntemler:** Etik kurul onayı alındıktan sonra Haziran 2016 ile Haziran 2019 tarihleri arasında siğil tanısı alan hastaların tıbbi dosyaları retrospektif olarak incelendi. Hastaların demografik ve klinik özellikleri kaydedildi. 6 seans sonrasında klinik olarak düzelmeyen hastalar tedaviye dirençli olarak kabul edildi. Tedaviye dirençli ve dirençli olmayan gruplar arasında demografik ve klinik özellikler SPSS 17 (Chicago, IL, USA) kullanılarak karşılaştırıldı, iki taraflı p değeri <0,05 istatistiksel olarak anlamlı kabul edildi. **Bulgular:** 98 hastanın 56'sı (%57.2) kadın, 42'si (%42.8) erkekti. Ortalama yaş 21.98±12.80 yıl idi. Tüm hastalardan 28'i (%28.6) tedaviye dirençli idi. Dirençli grupta K/E oranı 20/8 (%71,4/28,6), dirençli olmayan grupta 36/34 (%51,4/48,6) idi. Gruplar arasındaki fark istatistiksel olarak anlamlıydı (p=0.04). Siğil boyutları 0-4,9 mm, 5-10 mm, >10 mm olan hastalar karşılaştırılmış ve direnç oranları sırasıyla %14.7, %31.5, %60 olarak bulundu. Alt gruplar arasındaki fark istatistiksel olarak anlamlıydı (p=0.01). Her iki grubun yaş ortalaması, lezyon lokalizasyonu, lezyon sayısı, verruka alt tipi, hastalık süresi ve seans aralıkları benzer bulundu (p>0.05). **Sonuç:** Kadınlarda ve daha büyük siğilleri olan hastalarda tedavi başarısı daha düşük bulundu.

Keywords: Warts; cryotherapy; treatment failure; female

Anahtar Kelimeler: Siğiller; kriyoterapi; tedavi başarısızlığı; kadın

Viral warts are benign epithelial proliferations caused by the human papilloma virus (HPV) and most frequently affecting the hands and feet.^{1,2} Warts can heal spontaneously in time without

any treatment but sometimes especially plantar and palmar warts called “verruca” can be painful and they require treatment because they are contagious.

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In management of warts, the patient's immunologic status, cooperation and tolerance of adverse reactions are important factors that influence choice of treatment. The ideal therapy should be effective and cause minimal adverse effects. Various methods, such as destructive, virucidal, antimitotic and immunomodulatory treatments can be used in its treatment. Application of some topical agents (salicylic acid, cantharidin, podophyllin, podophylotoxin, 5-fluorouracil, bleomycin, imiquimod or interferons) and some physical destruction methods such as surgical excision, cryotherapy, electrodesiccation and laser therapy are mostly known treatment modalities.^{3,4}

Cryotherapy is a physician-applied procedure that has been increasingly used in recent years, and is preferred because of the rarity of serious complications. It is routinely applied in dermatology outpatient clinics because it is more convenient due to its advantages such as ease of post-treatment care and no restriction on daily activities.

Application of the cryogen induces skin and vascular damage, leading to both epidermal and dermal cellular necrosis. Liquid nitrogen is usually used as the cryogenic agent. This treatment usually require no anesthesia, cause little or no scarring and does not cause systemic or distant cutaneous side effects. Postinflammatory hypo-hyperpigmentation may be seen but they are mostly not permanent.⁵⁻¹²

There may be many factors that affect the success of the treatment of warts with the cryotherapy method. However, there are limited number of studies on this subject in our country and in the world, and the results are contradictory.¹³⁻¹⁹ In our study, we aimed to reveal how the age and gender of the patient, the type, number, duration, localization of warts and cryotherapy session intervals affect the success of treatment.

MATERIAL AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki. After the ethics committee approval (ethical committee no. 2019-48, date: 27.6.2019) had been received from University of Health Sciences Kocaeli Derince Training and Research Hospital Clinical Research Ethics Committee,

the research was started. The medical files of patients who had the diagnosis of wart, between June 2016 and June 2019 were analysed retrospectively. Since the patients were selected according to the information available in their files, attention was paid to whether the necessary information about their diseases was recorded in detail and whether cryotherapy was applied by the same dermatologist. Patients who had warts in only one anatomical region and whose cryotherapy treatment was initiated by us were included in the study. The age and gender of the patients, the type, number, size, localization of lesions, disease duration, frequency of cryotherapy applications were recorded.

The patients who had warts with more than one clinical types and localizations, who had other systemic and dermatologic diseases, who had immunosuppressive therapy, who had tried other therapies before, who had adjunctive therapy, who did not come for check-ups, who had quitted the treatment, and who were pregnant were excluded from the study.

On scan dates, the number of patients who received cryotherapy with the diagnosis of warts was 136. However, there were a total of 38 patients with insufficient or incomplete file information and who did not match the criteria to be included in the study. Therefore, the study was completed with 98 patients.

In our outpatient clinic, liquid nitrogen (Brymill Cryoset liquid nitrogen unit) is used for cryotherapy and it is applied directly on the wart with a spray gun. In each session, a double freezing-melting cycle is applied using the open spray technique, the gun head is kept 1-2 cm away from the skin surface. Cryogen is sprayed into the lesion center and spraying is continued for 10 or 20 seconds until a 5 mm circumferential freezing ring forms around the lesion.

Routinely cryotherapy treatment is performed by following all the rules in our outpatient clinic. This treatment is started by obtaining an informed consent form from the patients. Patients are informed about side effects such as pain and blistering formation that may occur during and after treatment. Even if cryotherapy is started, treatment is not continued in patients who cannot tolerate these conditions. Pa-

tients are also informed that warts are contagious, and the situations that increase the contagiousness are explained in detail. In addition, cryotherapy is not applied to patients with cold urticaria, cryoglobulinemia, cryofibrinogenemia, Raynaud's phenomenon and collagen tissue disease for whom cryotherapy is contraindicated.

There is no gold standard for the most effective application frequency in cryotherapy.¹⁷⁻¹⁹ In our polyclinic, we generally recommend applications for every 2 weeks. However, it was seen that there were patients in our group who came to treatment at various intervals and to evaluate the differences between them, the patients were divided into 5 groups (2-3-4 weeks and irregular intervals).

There is no clear information about when the patient should be considered resistant to treatment in the cryotherapy method but there are publications reporting that warts that do not heal after 4-6 sessions of treatment are considered resistant to treatment.⁹⁻¹⁸ Therefore, in our study, the warts that have not completely disappeared clinically and dermatoscopically after 6 sessions were considered resistant and additional treatments are recommended for these patients.

STATISTICAL ANALYSIS

We calculated the sample size by using the p 0.05 power analysis program. When the Type 1 error was accepted as 0.05, it was observed that a minimum of 97 patients should be included in the study for the power of the test to be within the confidence interval (CI) of 0.80. Demographic features of groups were analyzed by using descriptive statistics. Non-parametric continuous variables (duration of illness, number of sessions) were presented as medians (25-75 percentile). Categorical variables were presented as frequency and percentage. The differences between the groups were analyzed with Mann-Whitney U test for numerical variables that do not have a normal distribution. Fisher's exact and Yates chi-square tests were used to compare categorical variables between 2 groups. Estimated odds ratios (OR) with 95% CIs were calculated from logistic regression analyses. A 2-sided p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17 (IBM, Chicago, IL, USA).

RESULTS

In the our study group, 56 of 98 patients (57.2%) were female and 42 of them (42.8%) were male. The mean age was 21.98±12.80 (4-54) years. Demographic findings (age and gender) of the patients, the type, number, duration, localization of warts and cryotherapy session intervals were summarized in Table 1.

Among all patients, 28 (28.6%) of them were resistant to the therapy and in 70 (71.4%) of them com-

TABLE 1: Demographic and clinical features of the patients.

Characteristic	Value
Number of patients (n)	98
Age, (mean±SD)	21.98±12.80 (4-54 years)
Gender, female (n)/male (n)	56/42
Number of warts	n (%)
1-5	78 (79.6)
6-10	8 (8.2)
>11	12 (12.2)
Lesion localizations	n (%)
Feet	40 (40.8)
Hands	30 (30.6)
Face	14 (14.3)
Anogenital	9 (9.2)
Oral mucoza	1 (1)
Ekstremitis	2 (2)
Scalp	2 (2)
Subtype of wart	n (%)
Verruca vulgaris (palmar)	30 (30.6)
Verrucavulgaris (other body parts)	19 (19.4)
Verru plantaris	40 (40.8)
Verru anogenitalis	9 (9.2)
Size of warts	n (%)
0-4.9 mm	34 (34.7)
5-10 mm	54 (55.1)
>10 mm	10 (10.2)
Disease duration (month) median (25-75 percentile)	5 (3-12)
Disease duration (month) mean±SD (minimum-maximum)	10.09±14.4 (1-108)
Session intervals	n (%)
2 weeks	52 (53.1)
3 weeks	15 (15.3)
4 weeks	2 (2)
Irregular*	28 (28.6)
>1 month	1 (1)
Number of sessions (n) median (25-75 percentile)	4 (3-7)

SD: Standard deviation.

plete recovery was seen. Comparison of treatment-resistant and non-resistant patient groups according to demographic and clinical features were summarised in Table 2. When groups were compared in terms of the mean age, lesion localization, verruca subtype, lesion number, and the duration of the disease; the difference between them were not found significant ($p>0.05$). The mean age of the resistant group was higher, but this was not statistically significant. Lesions of the resistant group were mostly located on the feet. The resistance rate was higher in verruca

plantaris subtype, but the differences between the groups were not statistically significant ($p>0.05$). Similarly it was observed that as the number of lesions increased, the probability of resistance increased 1.705 times, but this situation was not statistically significant (OR: 1.705, $p>0.05$).

In resistant group, 20 patients were female (71.4%), and 8 patients were male (28.6%). In the other group, 36 patients were female (51.4%) while 34 patients were male (48.6%). The difference between 2 groups was statistically significant ($p<0.05$) (Table 2).

TABLE 2: Comparison of treatment-resistant and non-resistant patient groups according to demographic and clinical features.

	Resistant	Non-resistant	p value
Number of patients (n)	28	70	
Gender, female/male (n)	20/8	36/34	0.042
Age, year, (mean±SD)	24.35±15.22	21.04±11.68	0.529
Lesion localization	n (%)	n (%)	
Feet	14 (50)	26 (37.1)	0.70
Hands	9 (32.1)	21 (30)	
Face	2 (7.1)	12 (17.1)	
Anogenital	2 (7.1)	7 (10)	
Extremities	1 (3.6)	1 (1.4)	
Oral mucoza	0	1 (1.4)	
Scalp	0	2 (2.9)	
Subtype of warts	n (%)	n (%)	
Verruca vulgaris (palmar)	9 (32.1)	21 (30)	0.61
Verrucavulgaris (other parts of the body)	3 (10.7)	15 (22.8)	
Verruca plantaris	14 (50)	26 (37.1)	
Verruca anogenital	2 people 7.1	7 (10)	
Number of warts	n (%)	n (%)	
1-5	20 (71.4)	58 (82.9)	0.45
6-10	3 (10.7)	4 (7.1)	
>11	3 (17.9)	7 (10)	
Size of warts	n (%)	n (%)	
0-4.9 mm	5 (17.9)	29 (41.4)	0.01
5-10 mm	17 (60.7)	37 (52.9)	
>10 mm	6 (21.4)	4 (5.7)	
Session intervals	n (%)	n (%)	
2 weeks	14 (50)	38 (54.3)	0.21
3 weeks	2 (7.1)	13 (18.6)	
4 weeks	0	2 (2.9)	
Irregular*	12 (42.9)	16 (22.9)	
Disease duration, month, median (25-75 percentile)	5.5 (2.2-12)	5 (3-12)	0.62
Number of sessions, n, median (25-75 percentile)	8 (7-9)	4 (3-5)	0.00

*<2 weeks, 2-3-4 weeks, >1 month; SD: Standard deviation.

The relationship between gender and resistance to treatment was also evaluated by logistic regression analysis and it was observed that resistance was 2.99 times higher in women (OR: 2.99, $p=0.04$). Thereupon, male and female patients were compared in terms of age, lesion number, lesion size, lesion localization and session intervals, and both groups were found to be statistically similar ($p>0.05$).

When the patients were divided into subgroups according to the verruca size; in patients with wart sizes of >10 mm, 5-10 mm, 0-4.9 mm, resistance rates were found respectively 60%, 31.5%, 14.7%. It was observed that as the wart size decreased, the resistance to treatment decreased proportionally and the difference between the subgroups was statistically significant ($p<0.05$). According to logistic regression analysis that was done to clarify the effect of wart size on resistance formation, warts with a size of 5-10 mm were less resistant to treatment than warts with a size of >10 mm (OR=0.168, $p=0.02$). In warts smaller than 5 mm, less resistance was detected compared to warts with a size of 5-10 mm (OR=0.078, $p=0.03$).

DISCUSSION

In treatment of warts, it is aimed to remove the wart with no recurrence, to induce immunity and to produce minimal scar. Cryotherapy causes necrotic destruction in HPV-infected keratinocytes, a cell-mediated response develops, induces local inflammation and destroys the warts with minimal or no scar formation.³⁻¹⁵ For these reasons, cryotherapy gives us everything that we want to achieve in the treatment of warts.

However, despite properly applied cryotherapy, we see that warts heal more slowly than expected or may be resistant to treatment. So we tried to investigate how the patient's age, gender, lesion size, disease duration, lesion number, wart type and session intervals changed the effectiveness of the treatment.

There are limited studies evaluating how the age of the patient affects the success of treatment, and according to their results, it has been reported that the resistance rate increases with increasing age.^{9,13,14} In

our study, it was observed that the mean age of treatment-resistant cases was higher, but this was not statistically significant. Again, we saw that there are limited studies evaluating the effect of patient gender on treatment success. According to their results, patient gender was not reported as a factor affecting treatment success.^{9,13} Contrary to these previous studies, in our study group, the disease was found to be significantly resistant to treatment in female patients. In our study, we do not have objective data to explain why women are resistant to treatment. In terms of age, lesion number, lesion size, lesion localization and session intervals, male and female patients were found to be similar. We thought that, the accuracy of this finding, which was obtained for the first time in our study, should be supported by new studies and then new prospective studies should be conducted on its causes.

There are also limited studies evaluating how the wart size affects the success of treatment. Previous studies investigating this issue have reported that increasing lesion size adversely affects the efficacy of treatment.¹⁴⁻¹⁶ Consistent with other studies, in our study, it was observed that the resistance rate decreased significantly as the lesion diameter decreased. According to this result, the large size of the warts was considered as another factor negatively affecting the success of the treatment. We thought that the lesion size may be an indicator of viral load and higher viral load might have an effect on the success of treatment.

The duration of warts is another issue that needs to be evaluated. In some studies evaluating the effect of disease duration on treatment success, it has been reported that long-term disease is more resistant to treatment.^{9,14} On the other hand, Doğan and Şaşmaz reported that the effect of this factor on treatment success was not significant.¹³ Similarly, in our study, this factor does not seem to affect the success of treatment. Verrucas have the chance to heal spontaneously in individuals with a healthy immune system and good self-care. Generally, long-standing or non-healing lesions indicate adverse patient-related personal factors. In our study, self-care conditions of patients were unknown but our patients were selected from individuals without any systemic or im-

mune system disease. Therefore, we thought that, unless there is a significant condition affecting the immune system, it can be concluded that the duration of the lesion does not affect the success of the properly performed cryotherapy. However, it would be better, to support this result with new prospective studies.

Since the number of lesions can also be an indicator of viral load, we thought that its effect on treatment success should also be evaluated. The results of previous prospective studies on this subject are contradictory. Doğan and Şaşmaz reported that the number of warts did not affect the response to cryotherapy.¹³ Similarly, Uçak et al. reported that the high number of lesions may reduce the efficacy of treatment.¹⁴ In our study, the number of lesions seems to be ineffective on treatment success. Similarly, as with the duration of the lesion, in immunocompetent individuals, it can be concluded that the number of lesions does not affect the success of properly performed cryotherapy. However, it should be supported by new prospective studies.

About location or subtype of verruca, it was reported that the rate of resistance to treatment is higher in verruca plantaris.^{9,13} In our study, it was observed that resistance to treatment was higher in the verruca plantaris than in all other subtypes, We thought that a lesion located in the hyperkeratotic area might be more resistant to treatment. This situation could not be shown statistically in our study, but it should be re-evaluated with new prospective studies.

Session intervals may be another factor that may affect the success of the treatment and different results were reported regarding the most effective session interval.^{18,19} In a study, applications performed every 2 weeks, once in 3 weeks, and once in 4 weeks were compared, and it was reported that applications performed every 2 or 3 weeks could be more effective.¹⁷ Bourke et al. thought that the application intervals did not affect the number of sessions, but that more frequent application would shorten the treatment time. However, it has been reported that the application every 2 weeks will be more comfortable in terms of both the patient and the physician compared

to the application once a week.¹⁸ Uyar and Sacar also thought that a treatment performed every 7-8 days might be more advantageous in terms of giving results in a shorter time than an application at 2-3 week intervals.¹⁹ In our study group, the distribution of patients was not homogeneous among the subgroups that made according to session intervals. Although the difference between the groups was not statistically significant, the success rate was higher in the treatments applied every 3 weeks and every 2 weeks. We thought that, more prospective studies with homogeneously distributed groups are needed in this regard.

Since our study was retrospective there are some limitations. We could not evaluate some factors such as the recurrence rates and also self-care status of the patients. However, in our routine practice, we meticulously record patients' information and to be more reliable we excluded the patients with missing important informations in their files.

CONCLUSION

According to the results of our study, treatment success is negatively affected for large lesions and in female patients. Why patient gender affects treatment success, must be clarified by new prospective studies. On the other hand, although they were not statistically significant, in our results, resistance rates were higher in older patients, in verruca plantaris subtype and in patients with higher number of lesions. When we evaluate results of other previous studies, it was seen that there are still contradictions about all these factors. So we thought that patient age, number of lesions, wart localization may also affect the success of treatment and there is a need for larger prospective studies. Factors such as, session intervals and duration of disease seem to be ineffective on treatment success according to our patient group.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Nurşad Çiftci; **Design:** Nurşad Çiftci; **Control/Supervision:** Nurşad Çiftci; **Data Collection and/or Processing:** Nurşad Çiftci, Hatice Kaya Özden; **Analysis and/or Interpretation:** Nurşad Çiftci, Hatice Kaya Özden; **Literature Review:** Nurşad Çiftci, Hatice Kaya Özden; **Writing the Article:** Nurşad Çiftci, Hatice Kaya Özden; **Critical Review:** Nurşad Çiftci, Hatice Kaya Özden.

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