Original Investigation
Orijinal Araştırma

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A comparative study of tangential or vertical application of spray cryotherapy in warts treatment

Verruka tedavisinde sprey kriyoterapinin tanjansiyel veya vertikal uygulanmasının karşılaştırılması

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Abstract

Background and Design: Cryotherapy is an easy-to-apply and effective method in the treatment of warts. Numerous studies have been conducted on the effectiveness of cryotherapy in treating warts. However, in the literature, there is no comparative study on the treatment success, side effects, and superiority of vertical or tangential application to each other in spray cryotherapy. This study aims to compare both methods and to determine the ideal method for increasing patient compliance and treatment success in cryotherapy.
Materials and Methods: Between December 2014 and March 2016, 25 volunteer patients with 173 warts on both hands were applied spray cryotherapy with the vertical method in one hand and tangential method in the other. The patients were evaluated in terms of both treatment success and side effects at three-week intervals.
Results: The two methods did not differ in therapeutic efficacy (p>0.05). There was no difference between the two methods in terms of bullae (p=0.515) and hypopigmentation (p=0.709) formation. When the pain scores of two spray methods warts were compared according to warts diameters, the tangential application's pain score was lower in warts smaller than 2.5 mm (p=0.031). There was no significant difference in warts of other diameters (between 2.6-5.0 mm and greater than 5.0 mm) (p>0.05). Warts requiring three sessions of treatment (20/173) were compared in each session for pain scores. Regardless of the method, a significant decrease in pain score was found in each consecutive session (p<0.05).
Conclusion: This is the first study to compare spray cryotherapy's vertical or tangential application to the lesion. Based on the data of this study, tangential spray application is more comfortable than vertical application. Cryotherapy may be a more widely used method if tangential spray freezing becomes common.
Keywords: Cryotherapy, pain, wart

Öz

Amaç: Kriyoterapi verruka vulgaris tedavisinde kolay uygulanabilen, etkili bir yöntemdir. Verruka tedavisinde kriyoterapinin etkinliği ile ilgili çok sayıda araştırma yapılmıştır. Ancak literatürde, sprey kriyoterapinin vertikal (tam karşıdan) veya tanjansiyel (teğetsel) uygulamasının tedavi başarısı, yan etkileri ve birbirlerine üstünlükleri ile ilgili karşılaştırmalı bir çalışma bulunmamaktadır. Bu çalışmada her iki yöntem karşılaştırılıp, kriyoterapide hasta uyumu ve tedavi başarısının artırılması için ideal yöntemin tespit edilmesi amaçlanmıştır.
Gereç ve Yöntem: Aralık 2014-Mart 2016 ayları arasında hastanemizin Deri ve zührevi hastalıklar anabilim dalının küçük müdahale biriminde her iki elinde toplam 173 verruka vulgarisi bulunan 25 gönüllü hastanın bir elindeki verrukalara vertikal, diğer elindeki verrukalara tanjansiyel yöntemle sprey kriyoterapi uygulanmıştır. Hastalar üçer hafta aralarla yapılan vizitlerde hem tedavi başarısı hem de yan etkiler açısından değerlendirilmiştir.
Bulgular: Her iki yöntem arasında etkinlik açısından bir fark bulunamamıştır (p>0,05). Her iki yöntem arasında bül (p=0,515) ve hipopigmentasyon (p=0,709) oluşumu açısından da bir fark saptanmamıştır. Verrukalar boyutlarına göre sınıflandırılıp ağrı skorları karşılaştırıldığında 2,5 mm'den küçük verrukalarda tanjansiyel uygulamada ağrı skoru vertikale göre düşük bulundu (p=0,031). Diğer boyutlarda (2,6-5,0 mm arası ve 5,0 mm'den büyük) verrukalarda anlamlı bir fark bulunmadı (p>0,05). Üç seans tedavi gerektiren verrukaların (20/173), her bir seanstaki ağrı skorları karşılaştırılmıştır. Yöntem farklılığı gözetmeden üç ölçüm arasında (giderek azalan) anlamlı bir farklılık bulunmuştur (p<0,05).

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Sonuç: Bu çalışma, sprey kriyoterapinin lezyona vertikal veya tanjansiyel uygulamasının karşılaştırıldığı ilk çalışmadır. Bu araştırmadaki verilere dayanarak verruka vulgaris tedavisinde tanjansiyel uygulama, vertikal uygulamaya göre daha konforludur. Tanjansiyel uygulamanın yaygınlaşması ile kriyoterapi daha çok tercih edilen bir yöntem haline gelecektir.
Anahtar Kelimeler: Kriyoterapi, ağrı, verruka

Introduction

Cryotherapy is a treatment method based on tissue damage by local cold application[1,2]. In dermatology, it is applied to treat benign, premalignant, and malignant skin lesions. One of the most common indications is wart treatment[3].

Cryotherapy aims to create selective tissue necrosis by local cold application. The contact of the cryogen with the tissue initiates biological changes[4]. These changes, in turn, result in direct cell damage, disruption in cell microcirculation, vascular thrombosis and stasis, cellular anoxia, tissue damage and necrosis[2,5-7].

Three basic methods are used in cryotherapy: Cotton-tipped applicator, spray cryotherapy and cryoprobe. The most commonly used method is to hold the hand-held unit's spray tip upright and spray vertically to the lesion until the ice ball (ice formation) is formed (Figure 1). It is applied to form a freezing ring from the edge of the lesion: 1-2 mm in benign lesions, 2-3 mm in premalignant lesions, and 4-5 mm in malignant lesions[8]. Some hand-held cryotherapy devices (for example: Cry-Ac®, BrymillCryogenic Systems, Ellington, Connecticut, USA) have metal extended tips with 90-degree curved ends (named condyloma tips, bent) in the application set. These bent tips are primarily designed to freeze intraoral or intravaginal lesions. However, these tips can also be used for tangential freezing of raised lesions on other skin areas. Thus, raised lesions, e.g., warts, can be treated more effectively without causing damage to the surrounding normal tissue. Moreover, freezing may be less painful in tangential cryotherapy. However, there is no comparative study in the literature regarding the treatment success, side effects, and superiority of spray cryotherapy's vertical or tangential application to the lesion.

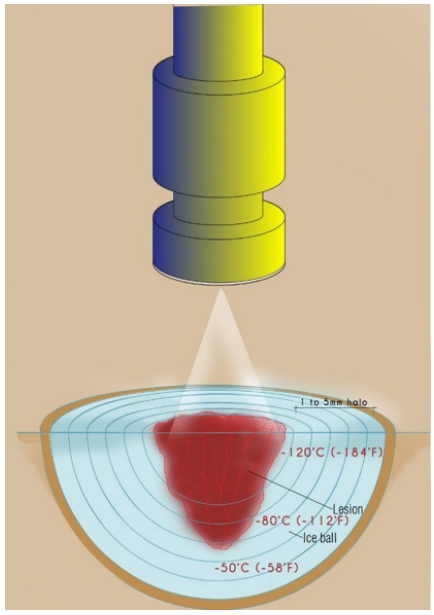

Figure 1. Ice ball formation and freezing depth in cryotherapy

To make the comparison mentioned above, patients with warts on both hands were selected. Spray cryotherapy was applied to the wart vertically on one hand and tangentially on the other of these patients. Both methods were compared in terms of "clinical effectiveness", "side effects," and "healing process". Thus, the aim is to determine the ideal method for increasing patient compliance and treatment success in cryotherapy.

Materials and Methods

For this study, the approval of the Ege University Faculty of Medicine Scientific Research Ethics Committee (approval number: 14-6/18, project number: B.30.2.EGE.0.20.05.00/OY/920/445, date: 03.07.2014). It was carried out in accordance with the principles of the "Helsinki Declaration".

Cases were chosen from patients who presented to our dermatology and venereal diseases department between December 2014 and March 2016 with the complaint of viral warts on both hands. They were also evaluated for inclusion and exclusion criteria (Table 1). The patients' age, gender, previous treatments, and history of immunosuppression and comorbidities were questioned. To exclude causes that may contraindicate cryotherapy application, a detailed dermatological examination of both hands was performed in terms of whole-body examination. Volunteers who met these criteria were informed about the study, and 27 patients participated in the study by reading and signing the informed consent form. Two of these patients were excluded from the study because they did not come for follow-up visits, and the study was completed with 25 patients. Age, gender, number of warts and dimensions (in mm) of each patient were recorded on the pre-prepared case form. Photographs of the warts were taken before each session and three months after the last session (Image 1). All patients were called for a control examination every three weeks. At each visit, the side effects of cryotherapy, such as bullae, erythema, and hypopigmentation were evaluated. Cryotherapy was performed in the dermatologic surgery unit of the dermatology department. The Cry-Ac® hand-held unit and spray tips (BrymillCryogenic Systems, Ellington, Connecticut, USA) were used as the cryosurgical device (Image 2). The warts on the left hand of the patients were frozen with 1-2 mm surrounding normal skin by classical vertical spray cryotherapy (Image 3). "D" tip was used for warts smaller than 0.5 cm, and "C" tip was used for larger ones. Tangential spray cryotherapy using the bend condyloma tip was applied to the warts of the patient's right hand. They were frozen until 1-2 mm surrounding skin frozen like those on the left hand. Each wart was raised above the skin level by squeezing it between the first and second fingers of the left hand. Thus, tangential freezing of the warts was facilitated (Image 4). A thin bent tip was used for warts smaller than 0.5 cm, and a thick bent tip for larger than 0.5 cm.

Pain felt by the patients during each cryotherapy session was evaluated with the "visual analogue scale" (VAS) ranging from "no pain: 0" to "worst pain: 10". "Picture pain scale" was used for pediatric patients. Pain scales are shown in Figure 2.

Table 1. Inclusion and exclusion criteria		
Inclusion criteria		
1. Warts on both hands		
2. Patients aged 12-65 years		
Exclusion criteria		
- Agammaglobulinemia	- Active infection	- Wart treatment in the last one month
- Cold intolerance	- Immunosuppression	- Neuropathy in the application area
- Cold urticaria	- Uncontrolled diabetes mellitus	- Presence of vascular insufficiency at the place of application
- Cryofibrinogenemia	- Multiple myeloma	- Wart in plantar and genital areas
- Cryoglobulinemia	- Raynaud's disease	

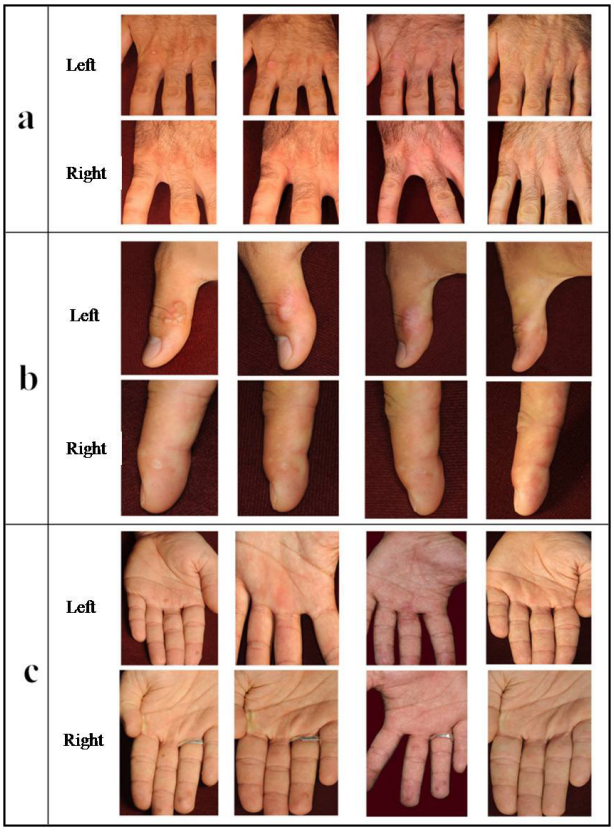

Image 1. Case pictures: **(a)** case number 11, **(b)** case 13, **(c)** case 16

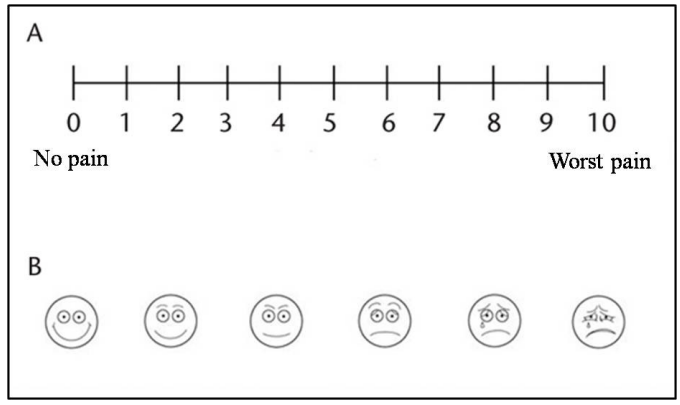

Figure 2. Pain scales: **(A)** Pain scale for adults, **(B)** pain scale for children

Image 2. Brymill Cry-Ac® spray cryotherapy gun and heads. The two spray heads on the far right were used for tangential cryotherapy

Statistical Analysis

The statistical analyses were performed by using IBM SPSS Statistics Version 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 21.0. Armonk, NY: IBM Corp). Normality of the distribution of the warts dimensions and the number of complete recovery sessions was verified with the Shapiro-Wilk test. Mann-Whitney U test was used to compare pain scores, bulla formation, and the number of complete healing sessions according to vertical or tangential spray application methods. Pain scores of warts treated in three sessions were compared with the Friedman test. Wilcoxon's signed rank test (SignedRank) was performed to compare pain scores in the first and second sessions. Spearman's rank correlation coefficient was used to analyze the correlations between method-size-pain variables. Cross-tables and chi-square analysis were applied to analyze erythema, bulla, hypopigmentation, complete healing, and recurrence according to the methods. Throughout the analyses, p-values of <0.05 were considered as statistically significant.

Results

Thirteen (52%) of the patients were male and 12 (48%) were female. The mean age of the patients was 25.2±2.0 years, and 60% were younger than 25 years.

The total number of treated warts (n) was 173; vertical spray cryotherapy was applied to 77 of these (44.5%) on the left hand (D),

and tangential (T) spray cryotherapy was applied to 96 of warts on the right hand (55.5%). The mean size of the 77 vertically sprayed lesions was 4.1±3.2 mm; the mean dimensions of the 96 tangential spray-applied lesions were 4.2±2.4 mm.

Of the 173 warts included in this study, 170 (98.3%) showed complete clinical cure. All of the 77 patients who underwent vertical spray cryotherapy showed complete recovery in a maximum of three sessions. Some 59.7% of these cases healed completely in the first session, 29.9% in the second session, and 10.4% in the third session. Ninety-tree (96.9%) of 96 patients who were applied tangential spray cryotherapy showed complete recovery after three sessions at the most. Approximately 47.9% of these cases healed completely in the first session, 40.6% in the second session, and 9.4% in the third session. When the application methods were compared, there was no statistically significant difference between the complete healing rates of the tangential and vertical spray cryotherapy methods and the number of healing sessions (p>0.05). During the control examinations, three months after full clinical recovery, 25 (14.7%) of the warts recurred. Thirteen (16.9%) of 77 cases were treated with vertical spray cryotherapy, and the difference between these values was not statistically significant (p=0.515).

Image 3. Vertical spray cryotherapy application (classical method)

Image 4. Tangential spray cryotherapy application

Twelve (12.9%) of 96 cases treated with tangential spray cryotherapy relapsed. The overall success rate of this study was calculated as 83.8% (145/173), 83.1% (64/77) for vertical spray cryotherapy, 84.3% (81/96) for tangential spray cryotherapy.

Regardless of the method, according to VAS, the pain score average for the lesions that underwent cryotherapy for three sessions was 5.8±1.6 in the first session, 4.5±1.5 in the second session, and 3.9±1.9 in the third session. It was determined that the pain score decreased significantly in each session. This decrease was found to be statistically significant (p<0.05). When the pain scores of both methods were compared according to VAS after each session, regardless of the size of the warts, no statistically significant difference was found (session one p=0.107, session two p=0.279, session three p=0.633). When the warts were classified according to their size (less than 2.5 mm, between 2.6 mm-5.0 mm and greater than 5.0 mm) and the pain scores of both methods were compared, the pain score was lower with the tangential application than with the vertical application. This difference was statistically significant, especially in warts smaller than 2.5 mm (p<0.05). A comparison of pain scores according to size and method is summarized in Table 2.

Discussion

Considering patient compliance, cotton-tipped applicators in pediatric patients and vertical spray cryotherapy in adult patients are generally recommended to treat warts. However, both methods have some disadvantages. The cotton-tipped applicator cannot provide sufficient depth in thick lesions[2,16]. Vertical spray application, on the other hand, does not have an equal effect on all parts of the lesion and damages the healthy tissue[17]. The tangential freezing was performed while squeezing the lesions g between the thumb and the second finger to raise the lesions. This squeezing of the lesion may have also had a positive effect on reducing the patient's perception of pain. It is also mentioned that pinching the skin with the fingers at the time local anethestetic injection helps decrease the patient's pain perception in the literature[18]. Although we could not find a statistically significant difference in clinical success between vertical and tangential spray freezing in this study, the pain score of tangential freezing was lower. Especially when the pain score was compared with the diameter of the treated wart, the tangential spray cryotherapy pain score was significantly lower as the diameter got smaller. This finding showed that the tangential application is painless and more comfortable than the vertical application.

Pain perception during cryotherapy depends on many physical factors such as the number of lesions, the location, freezing time, and the patient's pain threshold. Psychological factors such as informing the patient about the treatment, believing in the effectiveness of the treatment, and attitude towards the treatment method are also

Table 2. Pain score comparison by dimensions and methods

Criteria	Pain score/(n)		p-value
	V	T	
<2.5 mm	4.5±1.8/48	3.6±1.9/44	0.031
2.6-5.0 mm	5.2±1.9/54	4.5±1.9/89	0.086
<5 mm	6.3±2.2/14	5.9±1.4/26	0.399

important. The International Association for the Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with potential or actual tissue damage or any damage"[4,9]. Kissing children or blowing on their wounds reduces pain with a placebo effect[10]. In our study, pain scores in patients whose treatment lasted three sessions (20/173) decreased with each subsequent session, regardless of the treatment method. No significant relationship was also found between the sizes of the 20 warts and the decrease in pain scores. These data also show that the pain sensation is decreased in patients who are experienced in this procedure. However, more work is needed in this regard.

Complete recovery was observed in 145 (83.8%) of 173 warts treated with both spraying methods in our study. This recovery rate is higher than in the literature. For example, in the British Association of Dermatologists guidelines for managing cutaneous warts 2014, the cure rate with placebo and with cryosurgery was reported as 20-30%, and 49% (0-69%) respectively[11]. In the analysis performed on 107 patients by evaluating the Cochrane database, cryotherapy's effectiveness in treating warts was reported as 38.3%[12]. In this study, we attributed the higher success rate of cryotherapy for wart treatment than the literature to the long-term experience of cryotherapy in our clinic, the good compliance of the patients, and the relatively short follow-up period. However, it should be remembered that some of the warts may recur months or years after treatment.

There is no other study comparing vertical and tangential spray cryotherapy in the treatment of warts. However, there are comparative publications on how cryotherapy should be applied. It has been reported that long freezing time in cryotherapy increases the effectiveness of treatment, but causes more bullae and pain. Connolly et al.[13], in a randomized study with 200 patients with warts, compared 10 seconds of continuous spray cryotherapy with the classical method (freezing until a white frost ring forms around the lesion). They applied the freezing process once every two weeks for a maximum of five sessions, and 566 (56%) of 1,012 warts that were applied continuously for ten seconds and 539 (44%) of 1,232 warts frozen by the conventional method had complete recovery. However, this study observed less pain and less bulla formation with the classical method[13]. In our study, there was no difference in complications between vertical and tangential freezing (bulla and hypopigmentation).

In a Cochrane meta-analysis, when 592 warts were evaluated, aggressive cryotherapy (52.3%) was more effective than standard cryotherapy (30.9%)[12]. It has been reported that the double freezing cycle is not superior to a single cycle in hand-located warts[14]. In the study of Ahmed et al.[15] in which they evaluated 207 patients with warts on their hands and/or feet, they applied cryotherapy every two weeks for a maximum of three months; complete recovery was achieved in 47% of patients treated with the cotton-tipped applicator and 44% of patients treated with spray cryotherapy. No significant difference was found between the effectiveness of these two methods. In our study, there was no difference in efficacy between tangential/vertical spray cryotherapy.

Study Limitations

Our study limitation is that the study was conducted in a single-center.

Conclusion

This study revealed that tangential spray cryotherapy (especially in small warts) caused less pain than vertical spray. This method will provide patients a more painless treatment process, especially pediatric patients, and increase patient compliance.

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Ethics

Ethics Committee Approval: For this study, the approval of the Ege University Faculty of Medicine Scientific Research Ethics Committee (approval number: 14-6/18, project number: B.30.2.EGE.0.20.05.00/OY/920/445, date: 03.07.2014).

Informed Consent: Informed consent forms were obtained from all patients in accordance with the ethics committee.

Authorship Contributions

Surgical and Medical Practices: S.Y.Y., Concept: S.Y.Y., T.D., Design: S.Y.Y., T.D., Data Collection or Processing: S.Y.Y., Analysis or Interpretation: S.Y.Y., T.D., Literature Search: S.Y.Y., Writing: S.Y.Y., T.D.

Conflict of Interest: The authors declared that they have no conflict of interest.

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