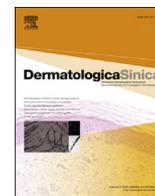




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BRIEF REPORT

Comparison of cryotherapy session intervals in the treatment of external genital warts



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ABSTRACT

A review of the literature found that the cryotherapy method used to treat external genital warts (EGWs) has been applied with varying intervals between sessions. However, no study has compared the intervals between sessions. The files of 312 patients who were diagnosed with genital warts and underwent cryotherapy were retrospectively reviewed. The patients were divided into two groups: 7–8 days between cryotherapy treatments and 14–21 days between cryotherapy treatments. The number of sessions and recurrence status were recorded for each patient. Cryotherapy methods applied with short intervals, such as 7–8 days, are more effective, requiring fewer sessions and less time when compared with longer intervals ($p < 0.0001$).

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Introduction

External genital warts (EGWs) are typically sexually transmitted benign epidermal growths caused by the human papilloma virus (HPV).¹ Various methods have been used for treatment, including imiquimod, trichloroacetic acid, podophyllotoxin, cryotherapy, electrocautery, topical or systemic interferons, laser surgery, podophyllin, and surgical excision. Various therapeutic protocols have been reported in EGW treatment.^{2,3} However, no specific treatment that is appropriate for all patients has been identified.

Cryotherapy is used to treat EGWs, but different session intervals have been reported in the literature.^{4–7} However, we found no comparative study that examined the session intervals.

We report on our experience with cryosurgery for the treatment of EGWs using different session intervals.

Methods

We retrospectively reviewed the files of 408 patients admitted to our polyclinic between January 2008 and January 2012. We recorded parameters including sex, age, previous treatment records, cryotherapy session intervals, number of sessions, adverse effects observed after cryotherapy, and recurrence after treatment. In September 2012, we phoned the 312 patients who underwent only

cryotherapy sessions and inquired about their current well-being and recurrence. We administered cryotherapy to treat EGWs in sessions with intervals of 2–3 weeks until August 2010. We then began to administer cryotherapy in sessions with intervals of 7–8 days. We divided the patients into two groups according to the session interval and evaluated the differences between groups.

Patients who did not receive any medical treatment for genital warts for at least 6 months were included in the study, and those with a history of keloid or cold sensitivity were excluded.

A liquid nitrogen spray (Cry-AC; Brymill Cryogenic Systems, Basingstoke, UK) was used to perform cryosurgery. The open spray technique was used for all patients. The patients received two freeze–thaw cycles in each session. We used nozzle C (0.06 mm) for all of the lesions, and continuous spraying was used for freezing according to wart size. The entirety of each lesion was frozen with a 1-mm margin (Figure 1). While freezing the tissue, a distance of 0.5–1 cm was maintained between the nozzle and the skin.

After the completion of treatment, the patients were asked to monitor themselves and to present to our clinic if they experienced any adverse effects. The patients who did not report recurrence were considered to be in remission.

Continuous variables are reported as the mean and standard deviation. Categorical data are reported as the number and percent. The Kolmogorov–Smirnov test was used to confirm a normal data distribution. The Student *t* test was used to compare continuous variables between groups. A *p* value < 0.05 was considered significant. Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences version 20.0; SPSS Inc., Chicago, IL, USA).

Conflicts of interest: The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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Figure 1 A view of the patient's genitalia immediately after the second session of cryotherapy application (8 days after the first session).

The study was approved by the institutional review board of the University of Sifa.

Results

In total, 254 males and 58 females were included in the study. The youngest patient was 18 years old, and the oldest was 61 years old; the mean age was 33.46 ± 8.811 years. Cryotherapy was administered to 207 patients (Group 1) with a 7–8-day interval and to 105 patients (Group 2) with a 14–21-day interval. Before admission to our clinic, 14 patients underwent electrocautery, 16 received cryotherapy, eight received both cryotherapy and electrocautery, seven received topical imiquimod cream, and 267 received no therapy. The patients underwent a minimum of two and a maximum of 25 sessions, with a mean of 6.90 ± 3.161 sessions. Group 1 underwent a mean of 6.04 ± 2.319 sessions, and Group 2 underwent a mean of 8.60 ± 3.852 sessions (Figure 2). Eight (4.34%) recurrences were observed in Group 1, but 23 patients in this group were lost to follow-up. Eleven (14.66%) recurrences were observed in Group 2, but 30 patients were lost to follow-up. We observed only three patients with recurrence after 6 months—one of them was in Group 1 (0.54%), two of them were in Group 2 (2.66%). Nearly every patient experienced blistering or hemorrhagic blistering, but none of the patients developed a permanent scar as a complication. Only five patients reported pigmentation changes at the site of cryotherapy—two of them were in Group 1 (1.08%), three of them were in Group 2 (4%). No difference was observed in long-term adverse effects.

Discussion

EGWs are benign epidermal growths caused by HPV. Genital warts are typically sexually transmitted; however, rare vertical transmission

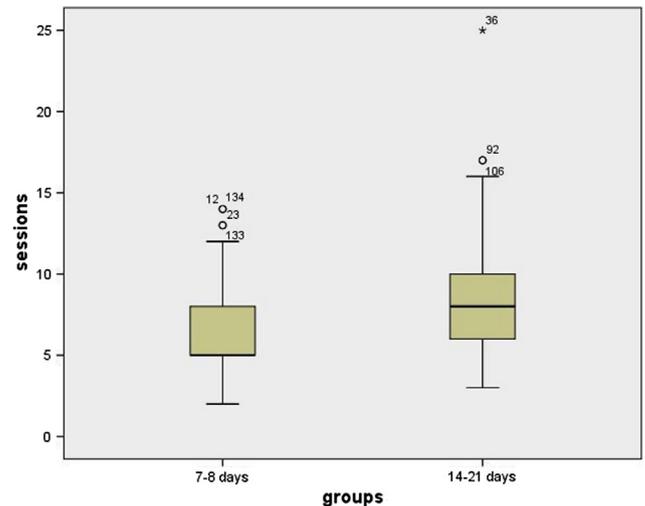


Figure 2 Distribution of the number of sessions administered to the groups.

and autoinoculation are also observed. Among all sexually transmitted diseases, anogenital HPV infections are the most prevalent worldwide. Each year, 30 million new cases are reported. There are various subclinical infections. Anogenital warts have a prevalence of 1–2% among sexually active individuals between the ages of 15 years and 49 years. Of the more than 100 HPV genotypes identified, nearly half cause infections in the genital tract.⁵

HPV types 6 and 11, which are believed to have a low risk, are the most common causes of genital warts. By contrast, HPV types 31, 33, 45, 51, 52, 56, 58, and 59 are considered to have an intermediate level of risk. These types cause squamous intraepithelial neoplasia and are considered less common causes of squamous cell carcinoma. Cervical dysplasia and anogenital cancers are strongly associated with HPV types 16 and 18. Patients who have visible genital warts can be infected simultaneously with multiple HPV types.⁹

Treatment protocols for genital warts use both surgical and nonsurgical methods. Nonsurgical treatment includes the application of local agents such as imiquimod, podophyllotoxin, and 5-fluorouracil. Other local agents used in outpatient treatment settings include trichloroacetic acid (TCA), podophyllin, and the intralesional application of agents such as interferon and bleomycin. Surgical methods include cryotherapy, electrosurgery, excision, and laser therapy, which primarily aim to remove visible lesions.

Wart clearance is generally accepted as the complete eradication of warts from the treated area, rather than the elimination of HPV. Although removal of HPV is not the primary goal of treatment, most patients who experience wart clearance will become HPV negative.¹⁰

Previous studies have reported a 79–88% rate of genital wart removal by cryotherapy alone or combined with other treatments. However, despite multiple therapies, 25–39% of cases report recurrences.^{11,12}

The rate of long-term regression remains unknown. Recurrence occurs in 25–67% of patients within 3 months after therapy in the areas previously treated for genital warts, and it is associated with the reactivation of long-lived cells at the treatment site. Risk factors for persistence include high-risk types of HPV and old age.¹²

The literature contains few studies that compare the various treatment methods and cryotherapy in the treatment of EGWs. In these studies, cryotherapy was used at different intervals.^{4–7} However, we were unable to find a comparative study on the session intervals. Youn et al administered cryotherapy to 560 patients with hand and foot viral warts at 2- and 3-week intervals.¹³ They concluded that a 2-week interval was optimal for cryotherapy, not

only due to a more rapid cure but also because of the considerably lower recurrence rate, the similar complication rate, and the longer mean time to recurrence than cryotherapy administered with a 3-week interval.

In the present study, a 7–8-day interval between cryotherapy sessions was found to be effective for EGWs in fewer sessions than a 14–21-day interval ($p < 0.0001$). The lower recurrence rate observed with the 7–8-day interval may have resulted from the early completion of treatment and longer follow-up period in Group 2. Additionally, when compared with other studies, the number of sessions in our study was higher, and the recurrence rate was lower. However, following the clinical clearance of warts, the patients were followed for 6 months, and any treatment administered for recurrences within this period was considered as a session.^{4,11,12} In our study, the number of males was higher than the number of females, but female patients typically prefer gynecology polyclinics. Patients in both of our treatment groups tolerated the procedure well. Although our study could not evaluate EGW intensity because this was a retrospective study, no deliberate preference was considered when placing patients in groups in terms of wart intensity because we divided the groups by treatment date. For future studies comparing cryotherapy with another EGW treatment, we suggest using short cryotherapy session intervals, for example, 7–8 days.

Conclusion

Our results support that shorter intervals between cryotherapy sessions, such as 7–8 days, can be effective in EGW treatment and require fewer sessions administered over a shorter time period. Thus applying cryotherapy with short intervals could increase the use of this cheap and widely used method.

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