



## Research Article

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# Sequential Therapy of Common and Plantar Warts with Salicylic Acid after Cryotherapy Versus Cryotherapy Alone: A Case-Control Study in 42 Subjects

Diotallevi F<sup>1</sup>, Milani M<sup>2\*</sup> and Offidani AM<sup>1</sup><sup>1</sup>Dermatological Clinic, Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Italy<sup>2</sup>Medical Department, Cantabria Labs Difa Cooper, Italy

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\*Corresponding author: Milani M, Medical Department, Difa Cooper Medical Direction, Via Milano 160, Caronno P (VA), Italy

## Abstract

**Background:** Common wart (CW; Verruca vulgaris) is a benign cutaneous virus infection caused by human papilloma virus commonly located in the palmar and plantar regions. Warts, especially located at pressure points, could be painful, but in general they are asymptomatic. Treatment is not always necessary but when multiple lesions, pain, immunosuppression and discomfort are present therapeutic intervention could be mandatory. Chemical or physical destructions are commonly used for the treatment of CW. Cryotherapy with liquid nitrogen is a common clinician-administered treatment. The most relevant drawbacks of this procedure are the pain associated with treatment, the need of several sessions and the recurrence of new lesion. Salicylic acid (SA) applied under tape occlusion is a convenient, effective, and safe therapy of CW, even if no effective as cryotherapy. So far, there are few data regarding the efficacy and safety of the sequential treatment of CW with cryotherapy followed by a 10-day treatment course with SA.

**Study Design:** We evaluated in a case-control study the clinical efficacy of cryotherapy alone and cryotherapy with SA in adult immunocompetent subjects with common or plantar warts.

**Subjects and Methods:** We evaluated a total of forty-two men and women, mean age 33±13 years, with CW located in the palm (30% of the lesions) and plantar (70%) regions. Twenty subjects (mean CW lesion number: 2.2±0.7) represented the cases group and twenty-two the control group. The cases subjects were treated with a cryotherapy session and after 3 days topical SA patch was applied for additional 10 consecutive days. The control group, after the initial cryotherapy session, was followed clinically to evaluate the need of new cryotherapy procedures. After the last cryotherapy, all subjects underwent to a follow up evaluation of three months.

**Results:** In the case group the sequential therapy was very effective with disappearance of the treated lesion. After the first cryotherapy session and the sequential SA treatment, the additional cryotherapy treatments were on average, mean ± SD, 1.4 ± 0.6 (range 1-3). In the control group, in order to obtain a complete cure of CW, the additional cryotherapy treatments were 3.4±0.7 (range 1-5). This difference was statistically significant (p=0.0001) in favour of the cases vs. control subjects. Only two subjects (both in the control group) suffered from recurrences in the follow up.

**Conclusion:** In subjects with CW, the sequential therapy with cryotherapy and topical salicylic acid is an effective strategy able to reduce significantly the need of additional cryotherapy procedures therefore reducing the procedure-associated discomfort. Furthermore, this sequential therapeutic strategy could offer additional benefits in term of cost-saving.

**Keywords:** Common warts; Cryotherapy; Salicylic acid; Case-control study

## Background

Common wart (CW; Verruca vulgaris) is a benign cutaneous virus infection caused by human papilloma virus (HPV) commonly located in the palm and plantar regions. HPV could infect skin

by direct and indirect contacts and the risk of transmission is increased when there is a macerated skin. CW is very common in children and young adults. Epidemiological data report that between 10 and 30% of school children present cutaneous

warts. Immunosuppression is also a relevant risk factor. CW are very delimited skin growth firm and rough hyperkeratotic papules or nodules and could be considered as self-limiting papilloma. Warts, especially located at pressure points, could be painful, but in general they are asymptomatic. Treatment is not always necessary but when multiple lesions, pain, discomfort, functional impairment, or immunosuppression are present a specific therapeutic intervention could be mandatory. Chemical or physical destructions are commonly used for the treatment of CW [1]. Cryotherapy with liquid nitrogen is a common clinician-administered treatment. The most relevant drawbacks of this procedure are the pain associated with treatment, the need of multiple sessions for complete resolution and the recurrence of new lesions. Salicylic acid (SA) applied under tape occlusion is a convenient, effective, and safe therapy of CW, even if no effective as cryotherapy. So far, there are few data regarding the efficacy and safety of the sequential treatment of CW with cryotherapy followed by a 10-day treatment course with SA [2]. This approach, at least theoretically, could increase the efficacy of the treatment strategy with a reduction of the number of cryotherapies needed to eliminate CW lesions.

### Study Design

We evaluated in a case-control study the clinical efficacy of cryotherapy alone in comparison with cryotherapy with sequential SA treatment in adult immunocompetent subjects with palm-plantar warts. The study was conducted according to Good Clinical practices procedures.

### Subjects and Methods

We evaluated a total of forty-two men and women, mean age 33±13 years, with CW located in the palmar (30% of the lesions) and plantar (70%) regions. Twenty subjects (mean CW lesions 2.2±0.7) represented the cases group and twenty-two the control group (mean CW lesions 1.2±0.5). The cases were treated with a cryotherapy session and after 3 days topical SA 15% patch (one application/day) was applied for additional 10 consecutive

days [3]. The control group, after the initial cryotherapy session, was followed clinically to evaluate the need of new cryotherapy procedures. Additional cryotherapy sessions were programmed every two weeks until all warts were completely gone. After the last cryotherapy, all subjects underwent to a follow up evaluation of three months. Cryotherapy session was performed as follow: a wad of cotton wool saturated with liquid nitrogen was applied on and around the wart until a frozen halo appeared (i.e. 15 sec) [4]. The SA application, (15% SA patches, Transversal™, Difa Cooper Italy) starting 3 days after the cryotherapy treatment, was made every day for 10 consecutive days. The wart lesion would be considered cured when no longer visible and palpable.

### Statistical Analysis

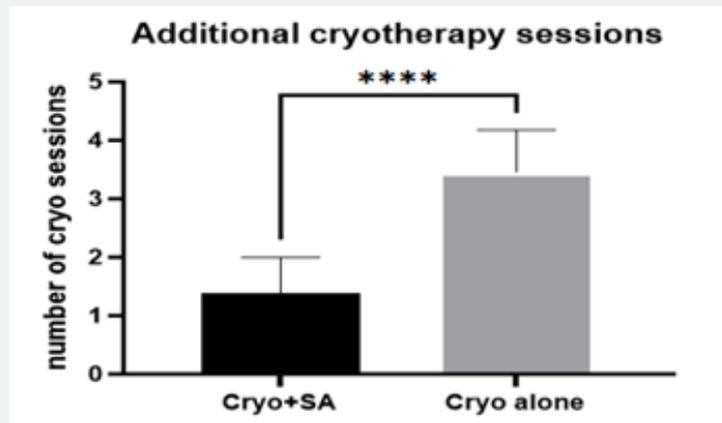
Statistical analysis was performed using GraphPad statistical software ver. 13.0 (La Jolla, CA, USA). Continuous variables were expressed as mean ± Standard Deviation (SD). The Mann-Whitney tests was used for the analysis of the primary outcome of the study [5-7]. We calculated the 95% Confidence intervals of the difference in the variables evaluated. According to the nature of a pilot study no sample size calculation was performed.

### Results

This case-control trial was performed in a University Dermatologic Clinic (Ancona Hospital) between September 2021 and May 2022. Table 1 shows the subjects characteristics of cases and controls. In the case group the sequential therapy was very effective with disappearance of all the treated lesions. After the first cryotherapy session and the sequential SA treatment, additional cryotherapy treatments were on average, mean±SD, 1.4±0.6 (range 1-3). In the control group the additional cryotherapy treatments were 3.4±0.7 (range 1-5) [8-10]. This difference was statistically significant (p=0.0001) (minus 2.2 sessions in comparison with controls; 95% CI of the difference: from 1.6 to 2.4) in favour of the cases vs. control subjects (Figure 1). Only two subjects (both in the control group) suffered from recurrences in the follow up.

**Table 1:** Subjects' characteristics at baseline.

	Number	Sex M/W	Age	Risk factors	Duration of warts in months mean±SD	Number of lesions before Cryotherapy, mean±SD	Localization of Warts
Cases	20	9/11	33	Yes in 7 subjects (35%)	5±7	2.2±0.7	Hand: 20 lesions Foot: 24 lesions
Controls	22	11/11	33	Yes in 7 subjects (32%)	4±8	1.2±0.5	Hand: 7 lesions Foot: 20 lesions



**Figure 1:** Number of cryotherapy sessions needed after the initial cryotherapy treatment in cases (Cryo+SA) and in controls (Cryo alone). \*\*\*\*:  $p=0.0001$ , Mann Whitney Test.

## Discussion

In this case-control study we found that the sequential strategy using cryotherapy followed by 10-day topical salicylic acid treatment is an effective therapeutic approach for palm-plantar CW [11-13]. The sequential use of SA after cryotherapy significantly reduces the need of additional cryotherapy sessions. This offers a dual advantage: the reduction of procedure-associated discomfort and pain for the patient and a direct and indirect cost saving effect [14-15]. The usual treatment of CW is cryotherapy with liquid nitrogen. Topical application of salicylic acid is an alternative approach with less procedure-associated pain and discomfort. Some trials suggest that cryotherapy is more effective than SA, however other evidence comparing these two therapeutic strategies showed no differences in effectiveness. A common problem with both treatments is the recurrency of CW lesions [16]. In addition, cryotherapy is considered an expensive option for the treatment of warts in primary care. Several cryotherapy treatments are usually required increasing the cost of the CW treatment. A session of cryotherapy has an average cost of 120 €. A sequential approach (using a course of SA topical application after an initial cryotherapy session) could increase the clinical effectiveness of the cryotherapy regimen [17]. So far, there are few data regarding the efficacy and safety of the sequential treatment approach of CW with cryotherapy followed by SA application. The main limitation is that the present study is a case-control trial [18-20]. Future controlled randomized studies are warranted to better evaluate the clinical efficacy of this sequential therapy approach for this very common skin disorder.

## Conclusion

In subjects with CW, the sequential therapy with cryotherapy and topical salicylic acid is an effective strategy able to significantly reduce the need of additional cryotherapy procedures therefore

reducing the procedure-associated discomfort. Furthermore, this sequential therapeutic strategy could offer additional benefit in term of cost-saving.

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