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Original Article

Efficacy of cryotherapy combined with topical cantharidin application versus cryotherapy and placebo in the treatment of verruca vulgaris: A randomized, controlled clinical trial

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Abstract

Objective To evaluate the efficacy of combined cantharidin and cryotherapy versus placebo and cryotherapy in common warts.

Methods This was a double-blind clinical trial conducted on 110 patients. Lesions in both groups underwent cryotherapy followed by topical solution of cantharidin and flexible collodion in case and control groups, respectively. Participants were assessed based on cure rate, adverse effects and recurrence rate.

Results Complete cure was achieved in cantharidin group after 3.4 treatment sessions vs. 4.7 in control group. In cantharidin group, higher prevalence of hyperpigmentation was reported but incidence of atrophic scar was lower than control group. Recurrence rate in both groups was not statistically meaningful.

Conclusion Cantharidin can be recommended as a safe and effective adjunct treatment in children and patients where other treatment modalities are contraindicated.

Key words
Common warts, cantharidin, cryotherapy.

Introduction

Wart is a common viral skin disease caused by more than 100 serotypes of human papilloma virus (HPV).[1,2] Prevalence of the disease varies between 10% to 20% in children and adolescents.[3] Spontaneous resolution occurs in most of the lesions after 1 to 2 years.[4] Because of impairment in function, cosmetic problem, concern about malignancy change, psychosocial issues and unpredictable course, treatment is advised.[5]

Currently, there is no standard treatment for wart and none of them is successful, completely. Main treatment modalities for warts include destructive methods (physical and chemical) such as salicylic acid, 5-fluorouracil, glutaraldehyde, podophyllin, formic acid,

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cryotherapy, electrosurgery, lasers and those treatments based upon immune system regulation like imiquimod, immunotherapy, interferon, retinoids and cimetidine.[6-8]

Cryotherapy is one of the most popular treatment methods because of its availability, easy application, inexpensiveness and rapid response rate.[5,9] It can induce cellular injury and selective tissue necrosis by ice crystal formation and vascular stasis. It should be applied with caution when using near cartilage, tendons and cutaneous nerve. Its application is contraindicated in patients with vascular impairment and history of cold intolerance, cold urticaria, cryofibrinogenemia and cryoglobulinemia. Cryotherapy, also, can lead to hypo/hyperpigmentation especially in darker skin phenotypes.[10]

Cantharidin is one of the topical drugs derived from the blister beetle which was approved by FDA in 1938 and has been used in the treatment of molluscum contagiosum since 1950.[11,12] Cantharidin leads to acantholysis and intraepidermal blister via degeneration of desmosomal attachments and intraepidermal acantholysis by release of serine proteases, activates apoptosis and induces cell cycle arrest.[13,14] Healing of the lesions will occur until 4 to 7 days with temporary erythema and postinflammatory hypopigmentation. Ultimately, it will be improved without any residual scar formation. Because of the drug toxicity, in 1997, it has been placed in a Bulk Substance List and recommended to be applied only in the office by physician.[13]

As cryotherapy alone fails to treat warts in many cases, combination therapy can be used in order to decrease adverse effects, number of treatment sessions and enhance efficacy. So we decided to evaluate the efficacy of cryotherapy combined with cantharidin versus cryotherapy with placebo in the treatment of verruca vulgaris.

Methods

This was a randomized double-blind clinical trial conducted in Afzalipour Hospital, Kerman University of Medical Sciences, Iran in a duration from April 2010 to May 2012.

After informed consent, patients were randomized into two groups by Minitab® 16 software (Minitab Inc.). Lesions with 6mm diameter were selected in order to evaluate treatment efficacy. Exclusion criteria included pregnancy, breast feeding, lesions in face, genitalia and periungual areas, age less than 5 years, patients with immunosuppressive and immunobullous diseases. This proposal was approved by ethical committee in Kerman University with ethical code as K/91/03.

Cantharidin solution in flexible collodion with 0.07% concentration (Canthacur, Paladinmanufacture®, Canada) as drug and flexible collodion solution as placebo stored in similar container, which were blind for physician to apply.

Demographic features were recorded in both groups. Cryotherapy with liquid nitrogen was applied as two freeze-thaw cycle by cotton swab until white halo formed at the periphery of the lesions. Then, one of the solutions was applied randomly on the lesions up to 1 millimeter beyond margins by cotton swab. Finally, lesions were covered with non-porous wound-tape for 24 hours, after that, tape was removed by physician and washed with water and soap.

If patients had severe pain or burning sensation during 24 hours, wound-tape was removed immediately and wound was washed with water and soap, moreover, at the next session, patients were asked to remove it after 4 or 6 hours. If a blister occurred, it was aspirated by insulin syringe and roof of the blister preserved for prevention of the infection.

Treatment sessions were repeated every two weeks until complete cure or 6 weeks, whichever occurred earlier. After complete cure, patients had followed up for 4 weeks in order to assessment of the recurrence rate. At each follow-up visit, number and size of the lesions and side effects were recorded.

Statistical analysis

Data were analyzed by PASW 18 software (IBM Corp., Armonk, NY, USA). Descriptive measures of central, scatter plot index were calculated. Chi-square test and student t test were used for comparison between cure rate, adverse effects and mean number of the sessions. According to previous studies and consideration of 90% power for this study, sample size was calculated 110 and *P* value less than 0.05 was defined as significant.

Results

One hundred and ten participants were enrolled in this study (**Figure 1**). Patients' age ranged from 5 to 52 years. Demographic features were not significantly different between two groups (sex, p=0.844 and age, p=0.667), [**Table 1**].

Common sites of the involvement were hands (43 in cantharidin and 40 in placebo), foot (7 in cantharidin and 10 in placebo group). Other locations were less frequently seen. Positive family history of wart was 14.5% in cantharidin

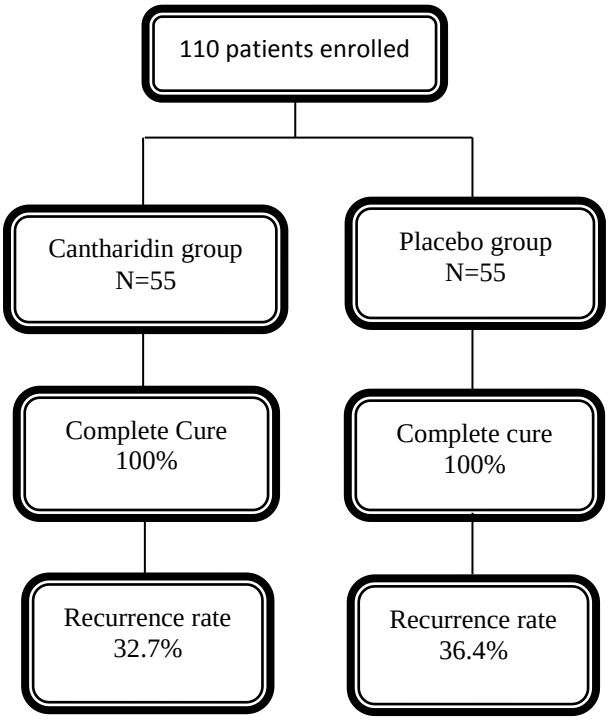

Figure 1 Clinical trial protocol and response rate.

group and 18.2%in placebo group. Mean number of the lesions in cantharidin group was 3.4 vs. 4.7 in placebo group (p<0.001).

Cure rate during treatment course in both groups has been shown in **Table 2**. Although 100% cure was seen in both groups, early treatment response was seen with cantharidin. After 3 treatment sessions, >50% patients were cured in cantharidin group in contrast to ~15% in the placebo group. However, recurrence rate in cantharidin and placebo group was 32.7% and 36.4%, respectively. Prevalence of the side effects has been demonstrated in **Table 3**.

Table 1 Demographic and pre-treatment features in both treatment groups.

		Cantharidin group	*Placebo group*
Sex	Female	20 (36.4%)	21 (38.2%)
	Male	35 (63.3%)	34 (61.8%)
Age (year)		20.8	21.6
Mean number of lesions		3.4	4.7

Table 2 Response rate in each treatment session in cantharidin group (n=55) and placebo group (n=55).

Treatment session	*Cantharidin group (%)*	*Placebo group (%)*
Two	3.6	3.6

Three	54.5	10.9
Four	32.7	25.5
Five	9.2	30.9
Six	0	29.1

Table 3 Frequency of complication in cantharidin group (n=55) and placebo group (n=55).

Complication	*Cantharidin group N (%)*	*Placebo group N (%)*	*X^2 square*	*P value*
Hyperpigmentation	16 (29.1)	6 (10.9)	5.682	0.017
Hypopigmentation	23 (41.8)	25 (45.5)	0.148	0.701
Severe pain	34 (61.8)	43 (78.2)	3.506	0.061
Blister formation	28 (50.9)	18 (32.7)	3.736	0.053
Atrophic scars	5 (9.1)	16 (29.1)	7.121	0.008
Itching sensation	7 (12.7)	5 (9.1)	0.374	0.541
Hypertrophic scars	4 (7.3)	2 (6.3)	0.705	0.401

Tolerable side effects like pain, blistering, pigmentary changes occurred in both groups, however, hyperpigmentation was statistically more frequent in the cantharidin group and atrophic scarring in the placebo group.

Discussion

Currently, several treatment modalities are available for verruca vulgaris, but none of them is completely satisfactory. Expensive cost, skin discoloration, scar formation, long period of the treatment and unavailability are some of the disadvantages of the treatment of wart lesions with these therapies.[6,15,16]

At present, cryotherapy is preferred as the second-line of the treatment. In a review article, Kwok reported a cure rate of 49% (0-64%) with cryotherapy.[17] In another clinical trial by Shamsi Meymandi *et al.*[18] efficacy of pulsed dye laser (PDL) and cryotherapy was compared on 100 wart lesions; clearance rate in cryotherapy group was reported 96% with mean treatment session of 2.8.[18]

Cantharidin is a vesicant and has been approved for treatment of warts and molluscum contagiosum. It has been used off-label in the treatment of callus,[19] leishmaniasis,[20] postherpetic neuralgia[21] and acquired perforating disorders.[22] In a study on verruca vulgaris by Flygare in 2008, cure rate in cantharidin and placebo group was estimated as 73.6% and 52.6%, respectively. In this study mean duration of treatment sessions in cantharidin was 3 vs. 4.7 in placebo group. These results are compatible with our study.[23]

Epstein *et al*.[24] analyzed 40 patients with 76 digital wart lesions treated with 0.7% cantharidin solution and equal mixture of acetone and flexible collodion and found that 56% of digital lesions and 33% of periungual lesions cured after only one treatment session. Finally, 57/61 digital wart lesions (93%) and 80% of periungual lesions in cantharidin group were cured after 3 or 4 treatment sessions. In this clinical trial, lesions were located in digital and periungual region that are relatively refractory to treatment. This can be a reason for lower improvement rate in this study relative to our study.[24]

Recently, this drug commonly has been used with other treatment modalities for wart, in order to increase efficacy and reduce treatment sessions. In one study in 2008, efficacy of mixture of cantharidin-podophyllotoxin-salicylic acid (CPS) with cryotherapy was evaluated. In this study 95.8% of the lesions responded to treatment in combination group and 86.8% of them were improved only after one treatment session. Lower treatment sessions in this study could be because of addition of salicylic acid

with keratolytic effect and podophyllotoxin that have antiviral effect.[25]

In another study in 2011 by Kacar,[26] CPS compound was compared with cryotherapy in plantar warts. CPS compound achieved clearance 100% vs. 41.7% in cryotherapy group, without statistical difference between two groups in complications rate.

In present study, complete cure rate was achieved in two groups. Mean number of the sessions in cantharidin and placebo group was 3.4 and 4.7, respectively. Thus, addition of cantharidin to cryotherapy led to significantly fewer treatment sessions.

Cantharidin is a better option in the treatment of warts for pediatric age group, because of absence of pain during the application. Development of blister and erosion can contribute to pain and itching sensation during 24 hours after cantharidin usage. This complication can be minimized by decreasing the time of drug application and occlusive dressing, using lower concentration of the compound, as well as, application of thin film layer of the drug instead of large amount. In our study application of cantharidin after cryotherapy, in spite of increasing bulla formation, was not consistent with more pain sensation (p=0.061).[27]

In other studies,[27,28] adverse effects such as pain, erythema, ring warts, postinflammatory hypo-/ hyperpigmentation, lymphangitis, secondary bacterial cellulitis and scarring have been reported after application of cantharidin. In our study combined treatment with cantharidin and cryotherapy led to reduced rate of both hypertrophic and atrophic scar (16.4% Vs. 35.4%) and incidence of atrophic scar was significantly lower in cantharidin group (9.1% vs. 29.1%, p=0.008). Hyperpigmentation was more common in cantharidin group (29.1%) than placebo (10.9%).

The strength of our study was double-blind randomization and limitation of our study was small sample size, so, we recommend larger clinical trial in order to better assessment response rate and adverse effects.

Conclusion

Our study results revealed that combination of cantharidin with cryotherapy results in a higher cure rate, lower treatment secessions and lesser side effects. Cantharidin can be used as a combination therapeutic option especially in children and those with recalcitrant lesions and contraindication of using other treatment modalities. Regarding the higher percentage of hyperpigmentation in cantharidin group, it should be applied with caution in sun-exposed sites especially in darker skin phenotypes.

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