

# Comparison of efficacy of cryotherapy versus Ionic Contraviral Therapy (ICVT) in the treatment of viral warts

Saadiya Siddiqui, Shahbaz Aman

Department of Dermatology, Services Institute of Medical Sciences, Services Hospital, Lahore.

## Abstract

**Background** Viral warts are common, benign, contagious dermatological condition for which various treatment modalities have been tried but recurrence and side effects are the limitations. We want to assess the efficacy of ionic contra viral therapy as an advance treatment.

**Objective** To compare the efficacy of cryotherapy versus ionic contra viral therapy (ICVT) in the treatment of viral warts.

**Methods** This randomized controlled trial was conducted on 80 patients of both genders, in the age range of 18-60 years, in the Department of Dermatology, Services Institute of Medical Sciences for the duration of 6 months. Patients having palmpoplantar warts participated in the study. Patients in group A were given Cryotherapy, while in group B Ionic contra viral therapy (digoxin + furosemide 0.125%). Patients in Group A were given Cryotherapy sessions once a week for four weeks while patients in Group B were offered to apply ICVT topically once daily for four week. Size of the individual lesion was measured before initiation of therapy, every week and at the end of the trial. The response was determined at the end of trial.

**Results** This randomized controlled trial included 80 patients, allocated into two groups comprising of 40 patients each. In Group-A patients were treated with Cryotherapy while Group-B patients were given ICVT. Mean age of patients in Group-A and in Group-B was  $27.45 \pm 14.07$  and  $27.65 \pm 11.14$  years, respectively. In Group-A 21 (52.5%) patients were male and 19(47.5%) patients were female and in Group-B also 21 (52.5%) were male and 19 (47.5%) were female. In Group-A total number of patients were 40 & total number of warts were 54 while in Group-B total number of patients was again 40 against which total number of warts were 87. In Group-A initial lesion size was  $0.34 \pm 0.18$ cm (mean value) and in Group-B it was  $0.44 \pm 0.21$ cm (mean value). Both groups showed decreasing trend in lesion size as treatment continued until 4th week. Mean lesion size at 4th week in Group-A and in Group-B was  $0.26 \pm 0.18$ cm and  $0.21 \pm 0.14$ cm, respectively. At 4th week in group A, excellent response rate was 70.37% (38 out of 54 lesions cleared) while in Group B excellent response rate was 68.97% (60 out of 87 lesions cleared). Although response to treatment was higher in Group-A patients in contrast to Group-B but it was not statistically significant (p-value=0.005).

**Conclusion** Ionic contra viral therapy is an effective new topical treatment modality and its results are comparable to cryotherapy in the treatment of viral warts.

## Key words

Cryotherapy, Ionic contra viral Therapy.

## Introduction

Cutaneous warts are common benign hyperkeratotic lesions due to infection of

keratinocytes with human papilloma virus.<sup>1</sup> Warts are contagious, can cause disfigurement and show tendency to koebnerize.<sup>2,3</sup> Cutaneous warts are prevalent in children and adults on an

average 3-13% but ranging up to 33% in primary school population.<sup>4</sup> Different HPV strains are responsible for specific types of warts such as common, flat, plantar, intermediate, mosaic, anogenital and oral varieties, among which HPV type 1, 2, 4 and 27 commonly cause plantar warts.<sup>5,6</sup> There are various treatment options available for treatment of viral warts including electrocauterization, cryotherapy, laser ablation, surgical excision. Among topical treatments salicylic acid, retinoic acid, podophyllin, 5-fluorouracil, interferon and imiquimod have been used but often treatment failure and recurrence are common end points.<sup>7</sup> Bacillus calmette-guerin vaccine, tuberculin, candida antigen, intralesional vitamin D3, human papilloma virus vaccines and auto implantation therapies are further immunotherapeutic agents used.<sup>2,8,9,10,11</sup> Some of these therapies are very time consuming and painful for the patient.<sup>7</sup> The goal of the treatment is to eliminate warts with no subsequent recurrence and disfigurement of the patient. However no single therapy guarantees lifelong immunity for cure of warts.<sup>7,12</sup>

The mechanism of cryotherapy is to freeze the viral wart at  $-196^{\circ}\text{C}$  leading to local inflammatory response by cell damage. It may result in hypopigmentation and pain.<sup>13,14</sup> In a quest to find suitable drug that may cure warts without pain and disfigurement, a new drug combination was tried that showed inhibitory effect on growth of DNA viruses. Human papilloma virus depends upon potassium ion inflow for its multiplication. Digoxin is a cardiac glycoside and furosemide is a loop diuretic. These two drugs work by causing inhibition of

K<sup>+</sup> ion inflow through cell membranes of viral particles by interacting with cell membrane ion cotransporters Na<sup>+</sup>/K<sup>+</sup> -ATPase and Na-K-Cl. In 2006 an invitro study supported the inhibitory role digoxin and furosemide on the growth of viral warts. This combination of two well known drugs was labelled as Ionic Contra Viral Therapy (ICVT). These two drugs when topically applied are very effective in treating viral warts.<sup>15-17</sup>

## Methods

It was a Randomized Controlled Trial conducted at Department of Dermatology, Services Institute of Medical Sciences Lahore for a duration of 6 months from 1<sup>st</sup> January 2018 to 30<sup>th</sup> June 2018. After approval from Ethical Review Committee & written informed consents, patients of both genders with ages from 18-60 years having palmar or plantar warts confirmed on clinical examination, were enrolled on the basis of non-probability consecutive sampling. Patients having warts more than six months period, received any other treatment for warts in last four weeks, suffering from ischemic heart disease, on immunosuppressive therapy, pregnant and lactating mothers were not included in the trial. All enrolled patients were randomized into group A and Group B, size of individual lesion was measured & photographs were taken. These participants were randomly divided into two treatment groups using lottery method. In Group A: *Cryotherapy*: liquid nitrogen gas was applied with spray cryo gun in two freeze thaw cycles each of fifteen seconds duration till freezing reaches 2 to 3 mm around the lesion in each thaw cycle. In Group B: *Ionic contra viral Therapy*: Digoxin+furosemide (0.125%) was applied on individual lesion once a day. Group A patients were treated with cryotherapy for 4 sessions one week apart, while in Group B patients applied topical ionic contra viral therapy

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### Address for correspondence

Dr. Saadiya Siddiqui, Senior Registrar,  
Department of Dermatology,  
Services Institute of Medical Sciences/  
Services Hospital, Lahore.  
Ph: 03334428320  
Email: saadiyas7@gmail.com

once daily for 4 consecutive weeks. Size of individual lesion was measured on once weekly follow up visit for 4 consecutive weeks. Final follow-up was done at the end of 4 weeks for patients of both groups to assess the efficacy of both treatment modalities. Response to treatment was recorded as poor (<30% clearance), satisfactory (>30-60% clearance), good (>60-90% clearance) and excellent (>90% clearance or complete removal of wart). All the data was collected on predesigned proforma & was analyzed in SPSS v.22. P value of less than 0.05 was considered as significant.

**RESULTS**

In this trial, 80 patients were included. These participants were divided into two groups of 40 each. In Group-A patients underwent Cryotherapy and in Group-B patients applied ICVT. Mean age of patients in Group-A and in Group-B was 27.45±14.07 years and 27.65±11.14 years. In group-A 21 (52.5%) patients were male and 19 (47.5%) patients were female meanwhile group B comprised of 21(52.5%) male and 19 (47.5%) female (Table 1).

In group-A total number of warts were 54 and in group B total number of warts was 87 (Table 2). In Group-A initial lesion size was 0.34±0.18 cm (mean) and in Group-B it was 0.44±0.21 cm (mean). Both groups showed decreasing trend in lesion size as treatment continues until 4<sup>th</sup> week. Mean lesion size at 4<sup>th</sup> week in Group-A and in Group-B was 0.26±0.18cm and 0.21±0.14cm, respectively. No statistically outstanding difference was seen in lesion size in both treatment groups (Table 2). Both groups showed decreasing trend in lesion size up till 4<sup>th</sup> week post treatment (Figure 1).

In group-A 1 (1.9%) lesion showed excellent response, 2 (3.7%) with good response, 13

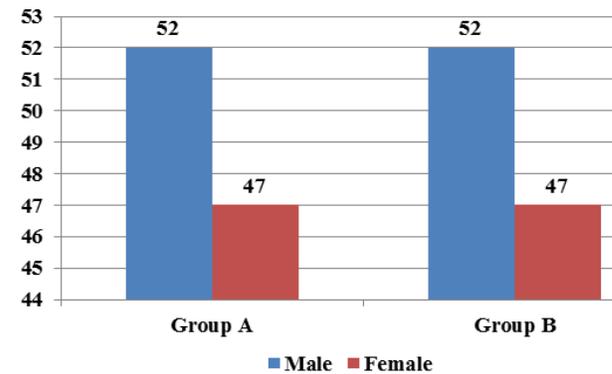
**Table 1** Patients characteristics in study groups.

	Group-A Cryotherapy (n=40)	Group-B ICVT (n=40)
Age (years)	27.45±14.07	27.65±11.14
Age Range	10-65	13-55
Male	21(52.5%)	21(52.5%)
Female	19(47.5%)	19(47.5%)

**Table 2** Lesion size in treatment groups.

Lesion	Group-A Cryotherapy	Group-B ICVT	p-value*
Number	54	87	
Initial size	0.34±0.18	0.44±0.21	0.010
1st Week	0.29±0.18	0.33±0.18	0.165
2nd Week	0.26±0.15	0.28±0.15	0.593
3rd Week	0.24±0.15	0.21±0.13	0.418
4th Week	0.26±0.18	0.21±0.14	0.343

Note: (\*) Independent Sample t-test.



**Figure 1** Gender distribution of patients in treatment groups.

(24.1%) with satisfactory and 38 (70.4%) lesions showed poor response. While in group-B 1 (1.1%) lesion showed excellent response, 35 (40.2%) showed satisfactory and 51 (58.6%) showed poor response. At 1<sup>st</sup> week post treatment, no notable difference was seen in efficacy of both treatment groups p-value=0.067 (Table 3). At 2<sup>nd</sup> and 3<sup>rd</sup> week post treatment, no outstanding difference was seen in efficacy of both treatment groups. However, at 4<sup>th</sup> week post treatment notable difference was seen in treatment efficacy of both groups p-value=0.005 (Table 4). At this point 70.4% lesions in group-A and 70.1% in group-B showed excellent treatment response, 7.4% in group-A and 20.7%

**Table 3** Efficacy of both treatments at 1<sup>st</sup> week of treatment.

Efficacy	Group A (n=40)	Group B (n=40)
	Number of lesions (%)	Number of lesions (%)
Excellent	1 (1.9%)	1 (1.1%)
Good	2 (3.7%)	0 (0%)
Satisfactory	13 (24.1%)	35 (40.2%)
Poor	38 (70.4%)	51 (58.6%)
Total	54 (100%)	87 (100%)

Chi Square=6.62 P Value=0.067

**Table 4** Efficacy of both treatments at 4<sup>th</sup> week of treatment.

Efficacy	Group A (n=40)	Group B (n=40)
	Number of lesions (%)	Number of lesions (%)
Excellent	38 (70.4%)	61 (70.1%)
Good	4 (7.4%)	18 (20.7%)
Satisfactory	10 (18.5%)	3 (3.4%)
Poor	2 (3.7%)	5 (5.8%)
Total	54 (100%)	87 (100%)

Chi Square=12.25 P Value=0.005

in group-B showed good treatment response, 18.5% in Group-A and 3.4% in group-B showed satisfactory response and 3.7% in group-A and 5.7% in group-B showed poor response (**Table 4**).

## Discussion

Cutaneous warts are benign, hyperkeratotic tumors caused by infection of keratinocytes with human papilloma virus, visible as well defined hyperkeratotic protrusions.<sup>1</sup> Plantar warts are one of its varieties, occurring commonly on pressure points of soles as skin colored papules with tiny black dots on its surface, one or few may occur.<sup>3,18</sup> There are many treatment options available which include topical therapies, physical destructive modalities, laser ablation, immune & auto implantation therapies.<sup>1,8-11</sup> All available treatment options are either time consuming or painful. Recurrences are also common.<sup>7,12</sup>



**Figure 3** Before

After



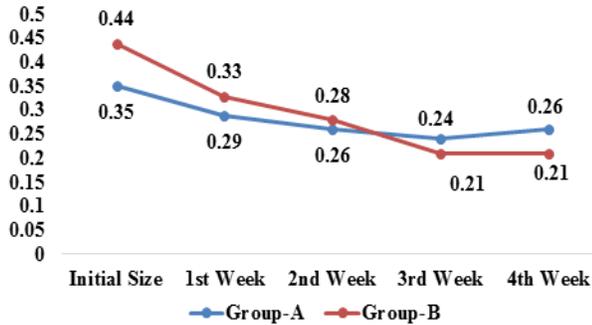
**Figure 4** Before

After

The concept of ICVT was introduced by Hartley et al. They confirmed the anti-viral properties of digoxin and furosemide in vitro<sup>16</sup>. Digoxin is a cardiac glycoside while furosemide is a loop diuretic. These drugs attach with cell membrane ion co-transporters Na<sup>+</sup>/K<sup>+</sup> ATPase and Na<sup>+</sup> K<sup>+</sup> 2Cl co-transporter 1.<sup>16</sup> Both these drug work by inhibition of K<sup>+</sup> ion influx which is crucial for DNA viruses replication inside host cells. This new combination of two drugs was then given the name of ionic contra viral therapy (ICVT) for further research.<sup>15,19</sup>

After this new concept, an open label study was conducted for first time in humans on twelve healthy subjects to assess the safety and tolerability of these two drugs on topical application. The results of this study showed no serious adverse events on topical application of this new drug combination.<sup>17</sup>

Keeping in view the efficacy, tolerability and



**Figure 2** Lesion size in treatment groups.

safety of these two drugs, we conducted a research and compared it with cryotherapy. Cryotherapy is one of the well established physical modality for the treatment of viral warts.<sup>4</sup>

In our study population mean age of patients in group A was  $27.45 \pm 14.07$  years while in group B it was  $27.65 \pm 11.14$  years (**Table 1**). While in the study conducted by Risberjen et al, on effect of ICVT, mean age of patients was  $23.8 \pm 7.9$  years.<sup>15</sup> In another comparative trial on cryotherapy and salicylic acid for treatment of warts conducted in Erbil Iraq, mean age of patient was  $22.45 \pm 8.72$  years.<sup>13</sup> Therefore age range of patients participating in these different trials is more or less similar to our study.

Our study population had similar gender distribution in both group A & group B (**Figure 1**). Among 80 participating patients, there were 21 males & 19 females in both groups. While in trial conducted by Risberjen et al out of eighty patients in total, there were 31 males and 49 females.<sup>15</sup> In the study conducted in Iraq out of 70 patients, there were 30 males and 40 females.<sup>13</sup> While another trial conducted by Bruggink SC et al, on effectiveness of monochloroacetic acid in comparison to cryotherapy for treating viral warts out of total 415 patients, there were 242 females and 173 males.<sup>20</sup> As apparently, there is a difference in

gender distribution in our study population from other trials discussed. So therefore we recommend further trials on a bigger sample size to evaluate this dissimilarity.

Our study results showed an overall decrease in lesion size in both groups (**Table 2**). Group A initial lesion size was  $0.34 \pm 0.18$ cm which was reduced to  $0.26 \pm 0.18$ cm at the end of treatment and in group B initial lesion size was  $0.44 \pm 0.21$ cm and the mean value at the end of treatment was reduced to  $0.21 \pm 0.14$ cm (**Figure 2**). So both therapies were comparable in decreasing lesion size and there was no statistically significant difference noted (**Table 2**). Similarly in the trial conducted by Risbergen et al, results revealed an overall decrease in size of 0.25cm (2.5mm) in the ICVT group, against the placebo group.<sup>15</sup>

In the beginning of study, only one patient in each group showed excellent response with >90% clearance in wart. Total 13 patients showed satisfactory response (>30-60% clearance) in group A and 35 patients showed satisfactory response in Group B (**Table 3**). But as the trial continued, the number of patients showing excellent, satisfactory or good response steadily increased in both groups. The percentage of patients having poor response from either treatment decreased at the end of treatment (**Table 3**). At the end of treatment 70.4% patients showed excellent response (>90% or complete clearance of wart) in group A, while in group B 70.1% patients showed excellent response to the topical ICVT applied. Both treatment modalities were efficacious with p value 0.005 (**Table 3**). The efficacy of ICVT in terms of wart clearance (100% reduction in wart size) in the trial conducted by Risberjen et al, was 57.44% (27 warts cleared out of 47).<sup>15</sup> Our results of ICVT group are comparatively higher as compared to this because of more number of warts in a bigger sample size (87 wart

in 40 patients of group B). In study conducted by Bruggink et al, effectiveness of cryotherapy against topical monochloroacetic acid was 54% (50 were cured out of 93).<sup>20</sup> While in the study conducted on Iraqi population of Erbil, the patients who received cryotherapy showed a response rate of 66.7% (20 cured out of 35) against salicylic acid group in which response rate was 80% (24 cured out of 35).<sup>13</sup> So we can say effectiveness of cryotherapy remained slightly less as compared against different treatment modalities among different trials. Therefore, ionic contra viral therapy should be tested against different treatment modalities, for a clearer picture regarding its efficacy as a new treatment for viral warts. During the course of study none of our patients reported any serious adverse event and ICVT was well tolerated.

### Conclusion

Ionic contra viral therapy is an effective new modality in the treatment of viral warts and results of its efficacy are comparable to Cryotherapy. Hence, we recommend further trials of ICVT against different treatment modalities for the treatment of viral warts.

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