

# Imiquimod vs Cryotherapy in the Treatment of Genital Warts: A Comparative Study

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## ABSTRACT

**Introduction:** Warts are the most easily recognized symptom of genital HPV infection. Genital warts are sexually transmitted disease caused by some types of human papillomavirus (HPV). Study was done to compare the efficacy of 5% imiquimod vs cryotherapy in the treatment of genital warts, to evaluate any adverse reactions occurred due to treatment and to evaluate any recurrences after treatment.

**Material and methods:** Cases of genital warts attending the Department of DVL, osmania general Hospital for a Duration of 24 months from January 2016 to December 2017. Sample size: Total 40 patients, 20 in each group.

**Results:** On comparison of clearance weeks and the treatment given it was observed that there was a significantly higher and early clearance rate with cryotherapy  $p < 0.05$ . There was no significant difference in occurrence of adverse reaction in either of treatment groups statistically ( $p > 0.05$ ). Recurrence was observed in 10% cases of cryotherapy group and there were no recurrence reported in imiquimod group in the present study.

**Conclusion:** Clearance of warts with Imiquimod takes long time when compared to cryotherapy. Occurrence of adverse reactions is almost equal in two groups. Recurrence reported in cryotherapy but not in Imiquimod group.

**Keywords:** Imiquimod vs Cryotherapy, Genital Warts

## INTRODUCTION

Warts are the most easily recognized symptom of genital HPV infection. Genital warts are sexually transmitted disease caused by some types of human papillomavirus (HPV). About 90% of those who contract HPV will not develop genital warts. HPV types 6 and 11 are most frequently the cause of genital warts.

It is spread through direct skin-to-skin contact, usually during oral, genital, or anal sex with an infected partner. While some types of HPV cause cervical cancer and anal cancers, these are not the same types of HPV that cause genital warts.<sup>1</sup>

About 80% of those infected are between the ages of 17–33. Although treatments can remove the warts, they do not remove the HPV, so warts can recur after treatment (about 50–73% of the time).<sup>2</sup> Warts can also spontaneously regress (with or without treatment).

Although 90% of HPV infections are cleared by the body within two years of infection, it is possible for infected cells to undergo a latency (quiet) period, with the first occurrence or a recurrence of symptoms happening months or years later.

Anal or genital warts may be transmitted during birth. The presence of wart-like lesions on the genitals of young

children has been suggested as an indicator of sexual abuse. However, genital warts can sometimes result from auto inoculated by warts elsewhere on the body, such as from the hands.<sup>3</sup>

The diagnosis of genital warts is most often made visually, but may require confirmation by biopsy in some cases.<sup>4</sup> Treatments can be classified as either physically ablative, or topical agents.

Study was done to compare the efficacy of 5% imiquimod vs cryotherapy in the treatment of genital warts, to evaluate any adverse reactions occurred due to treatment and to evaluate any recurrences after treatment.

## MATERIAL AND METHODS

Study was done on cases of genital warts attending the Department of DVL, Osmania General Hospital for period of 24 months from January 2016 to December 2017 on total 40 patients, 20 in each group.

### Inclusion criteria

All patients with genital warts, attending STD Clinic & DVL OP, in Osmania General Hospital

### Exclusion criteria

- Pregnant and nursing women
- Patients with HIV seropositivity
- Patients who are unable to return for follow up visits or comply with the protocol.

### Method of collection of data

Informed consent was taken from all the patients included in the study after clinical diagnosis. Patients were examined for number and size of warts. location of warts along with data regarding wart size type and number were recorded. In case of multiple warts the average size of all the warts was calculated for assessing response. Biopsy of the lesions

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was done to confirm the diagnosis, if required. Lesions were photographed with permission before starting the procedure. Patients were randomized into two groups of 20 each. One group was named 1 that received 5% Imiquimod and another group was named 2 that received cryotherapy with liquid nitrogen. The therapy was continued until completion of 12 weeks or till the lesions clear whichever was earlier. End point of the study was 12 weeks after inclusion in the study. All adverse events were recorded at each visit and at the end of study

**Procedure of application of imiquimod:** All patients gave written informed consent before enrolment. Before bedtime, patients rubbed the study cream into clean, dry, lesional skin until it disappeared and washed the area with soap and water  $8 \pm 2$  h after application. In our study, we trained the patients in the method of application of imiquimod in the first episode of application & advised them to apply the cream weekly thrice at bed time on alternate days. Their level of understanding regarding application of imiquimod was checked before they left the hospital. All their concerns regarding application of imiquimod were addressed.

**Procedure of application of cryotherapy:** In present study we gave cryotherapy using liquid nitrogen, at a temperature of  $-196^\circ$  c, with cryogun. Pre treatment photographs were taken. written informed consent is also taken.

The area to be treated is first cleaned using povidone iodine. Topical anaesthesia cream containing lidocaine & prilocaine combination is applied one hour before the procedure.

We used *Timed Spot Freeze Technique*, this method involves spraying of cryogen from a hand held gun device that holds about 300 ml of liquid nitrogen. Nozzle is held at a distance of 1cm from the surface of the lesion, trigger is pressed & cryogen is sprayed until an ice field is formed that includes the lesion and a rim of normal skin around it. The rim should ideally be 1-2mm, this ensues adequate destruction of the lesions. once the ice field is formed the spray should be continued for adequate time (holding time), later it is allowed to thaw completely this cycle is repeated 2-3 times. we used both direct freeze method & open spray method. we repeated the procedure every 2 weeks. Post treatment photographs were taken, any adverse reactions were noted down. We kept the patients on analgesics and topical mupirocin cream for 5 days after the procedure. We followed up the patient till 12 weeks.

## STATISTICAL ANALYSIS

The data obtained was analyzed using SPSS version 17.0. Continuous variables were expressed as mean  $\pm$  SD values. Appropriate statistical tests were used to compare efficacy of 5% imiquimod and cryotherapy in treatment of genital warts. Probability value (p value) was used to determine the level of significance p value  $< 0.05$  was considered as significant, p value  $< 0.01$  was considered as highly significant.

## RESULTS

The present study was undertaken in the Department of

Dermatology venereology & leprosy, Osmania Medical College and hospital, Hyderabad.

A total of 40 patients diagnosed with genital warts, attending dermatology OPD at OGH were recruited for the present study. After obtaining informed consent detailed history and medical examination was done. Patients were randomly

Age group in years	Imiquimod		Cryotherapy	
	Number	%	Number	%
16 – 20	1	5	1	5
21 – 25	8	40	7	35
26 – 30	5	25	5	25
31 – 35	1	5	4	20
36 – 40	3	15	2	10
41 – 45	2	10	1	5
Total	20	100	20	100
Chi square		6.53	P value	0.768

**Table-1:** Distribution of subjects by Age group

Age	Imiquimod		Cryotherapy	
	Mean	SD	Mean	SD
Age	29.5	7.43	29	6.5
F value	0.567		P value	0.571

**Table-2:** comparison of mean age between study group

Gender	Imiquimod		Cryotherapy	
	Number	%	Number	%
Male	18	90	13	65
Female	2	10	7	35
Total	20	100	20	100
Chi square	4.37		P value	0.112

**Table-3:** Distribution of patients based on gender

Marital status	Imiquimod		Cryotherapy	
	Number	%	Number	%
Married	15	75	15	75
Unmarried	5	25	5	25
Total	20	100	20	100
Chi square	1.429		P value	0.49

**Table-4:** Distribution of patients based on Marital status

Adverse Reaction	Imiquimod		Cryotherapy	
	Number	%	Number	%
Present	2	10.5	2	10
Absent	17	89.5	18	90
Total	19	100	20	100
Chi square	0.012		P value	0.99

**Table-5:** Relation between adverse reaction and treatment given

Recurrence	Imiquimod		Cryotherapy	
	Number	%	Number	%
Present	0	0	2	10
Absent	19	100	18	90
Total	19	100	20	100
Chi square	2.17		P value	0.338

**Table-6:** Relation between recurrences and treatment given

Clearance rate	Imiquimod		Cryotherapy	
	Number	%	Number	%
4 weeks	0	0	5	25
8 weeks	5	26.3	10	50
12 weeks	10	52.6	0	0
No clearance in 12 wks	4	21.1	5	25
Total	19	100	20	100
Chi square		26.7	P value	<0.001

**Table-7:** comparison between clearance and treatment given

H/O of risk exposure	Imiquimod		Cryotherapy	
	Number	%	Number	%
Present	4	20	4	20
Absent	16	80	16	80
Total	20	100	20	100
	Chi square	7.55	P value	0.023

**Table-8:** Relation between history of risk exposure and treatment given

distributed into Two groups of 20 patients each. Group 1 received received 5% imiquimod and group 2 received cryotherapy (table-1).

In the present study it was observed that majority of patients were in the age group of 21 to 25 and 26 – 30 yrs there was no statistically significant difference in distribution of patients based on age  $p > 0.05$  (table-2). Mean age was compared using one way Anova there was no statistically significant difference observed between groups  $p > 0.05$  (table-3). In the present study it was observed that 90 % males in imiquimod and 65 % males in cryotherapy group. There was no statistically significant difference in distribution of patients based on gender  $p > 0.05$  (table-4).

In the present study it was observed that married population more compared to unmarried population. There was no significant distribution of patients based on marital status  $p > 0.05$  (table -5). Adverse reactions were 10.5 % in imiquimod group and 10 % in cryotherapy group. There was no statistically significant difference in occurrence of adverse reaction in either of treatment groups  $p > 0.05$  (table-6). Recurrence was observed in 10 % cases of cryotherapy there were no recurrence reported in imiquimod group in the present study however there was no statistically significant difference in either of the groups  $p > 0.05$  (table-7). In the present study 1 patient in imiquimod who did not turn up for follow up was excluded from statistical analysis. On comparison of clearance rate and the treatment given it was observed that 25 % patients treated with cryotherapy achieved clearance at 4 week compared to 0 % treated with imiquimod. 50% patients treated with cryotherapy achieved clearance at 8 week compared to 26.3% treated with imiquimod. 52.6% patients treated with imiquimod achieved clearance at 12 weeks compared to 0% patients treated with cryotherapy. 21.1% patients in imiquimod group and 25% patients in cryotherapy group achieved incomplete clearance even at 12 week. There was a significantly higher and early clearance rate with cryotherapy ( $p < 0.05$ ) (table-8). In the

present study it was observed that patients with history of risk exposure was equal in both Imiquimod and cryotherapy group  $p < 0.05$ .

## DISCUSSION

The present study was undertaken in the Department of DVL (Dermatology venereology & leprosy), Osmania Medical College and hospital, Hyderabad.

A total of 40 patients diagnosed with genital warts, attending DVL OPD at OGH were recruited for the present study. After obtaining informed consent detailed history and medical examination was done. Patients were randomly distributed into two groups of 20 patients each. Group 1 received 5 % imiquimod, group 2 received cryotherapy.

**Age wise incidence of genital warts:** In present study most of the patients are in the age group of 21 to 30.

**In imiquimod group:** 5% are in 16-20, 40% are in 21-25, 25% are in 26-30, 5% are in 31-35, 15% are in 36-40, 10% are in 41-45. mean age in this group is 29.5.

In a study conducted by Neerja puri et al<sup>5</sup> at Kolkata, A study on the use of imiquimod for the treatment of genital molluscum contagiosum and genital warts in female patients, the commonest (48%) age group of patients was between 30 and 40 years, followed by 24% between 20 and 30 years, followed by 20% between 40 and 50 years, followed by 6% between 50 and 60 years and 2% between 10 and 20 years.

Current evidence suggests that over 50% of sexually active adults (15–25 years of age) have been infected with one or more HPV types. In the United States, the estimated prevalence among men and women between 15 and 49 years of age with genital warts is 1.4 million and with subclinical infection is 19 million. The mean age among males was 26 years and among females, 24 years, with a male-to-female ratio of 2:1.

The prevalence of HPV infection has risen steadily in the past 35 years, with as many as 20 million people in the United States believed to be infected.<sup>6,7</sup>

This phenomenon is often attributed to both an earlier age of initial sexual contact as well as an increase in the total number of sexual partners. Accordingly, nearly half of these new infections will occur in young adults ages 15 to 24 years.<sup>8</sup>

HPV is a highly contagious virus and is transmitted predominantly through oral, anal, and genital sexual contact, although rare instances of vertical transmission and autoinoculation have been reported.<sup>9</sup>

Additional risk factors include unprotected intercourse, use of oral contraceptives, a history of sexually transmitted infections, smoking, or immunosuppression.<sup>10,11</sup>

In present study imiquimod group, 65% were in 20-30, 20% were in 30-40, 10% were in 41- 45. In Neerja et al study commonest age group is 30 to 40 yrs, which is not correlating with present study.<sup>5</sup>

**In cryotherapy group:** 5% were in 16-20, 35% were in 21-25, 25% were in 26-30, 20% were in 31-35, 10% were in 36-40, 5% were in 41-45. Mean age in this group was 29 yrs.

**Gender distribution:** Imiquimod group had 90% male patients and 10% female patients. In cryotherapy 65% were male patients, 35% were female patients.

Majority of the patients in present study were male patients. In the present study it was observed that 90% males in imiquimod and 65% males in cryotherapy group.

Males were more because increased chance of exposure, most of the lesions on male genitalia are easily visible, and increased awareness, accessibility to health care.

Incidence in females is less because less chance of exposure, lesions are not visible easily especially warts inside the vagina, and on cervix, most of the warts are asymptomatic and subclinical infections are also high in female. Less accessibility to health care & lack of awareness regarding treatment modalities & social stigma.

Combined treatment of anogenital HPV infection with cryodestruction, podophyllin 25% and post-ablation immunomodulation with sinecatechins 15% ointment – a retrospective analysis; a study conducted by Mark E Juhl et al<sup>12</sup>, most of the pts are male only, which is correlating with our study.

**Marital status:** In present study married people in imiquimod group are 75%, in cryotherapy group are 75%. Unmarried people in imiquimod group are 25%, in cryotherapy group are 25%. In present study married patients were more than unmarried patients.

**History of risky sexual exposure:** In present study history of HRSE was present in 20% in imiquimod group, 20% in cryotherapy group.

HRSE was absent in 80% in imiquimod group, 80% in cryotherapy group.

In imiquimod & cryotherapy groups patients without HRSE were more compared to with HRSE.

**Clearance rates of warts:** In present study clearance rates of warts In imiquimod group were 0% at 4 weeks, 26.3% at 8 weeks, 52.6% at 12 weeks, totally clearance with imiquimod was 78.9%. In cryotherapy with liquid nitrogen group were 26.3% at 4 weeks, 52.6% at 8 weeks, 0% at 12 weeks totally clearance with cryotherapy was 78.9%.

Persistence of lesions at the end of 12 weeks with imiquimod was 21.1%, with cryotherapy was 21.1%.

According to present study there was no much difference in clearance of warts in between two groups; in cryotherapy group clearance of warts occurred early compared to imiquimod group. Clearance of warts with imiquimod and cryotherapy were equal, but clearance with imiquimod took longer time as it is a immunomodulator. So with imiquimod maximum clearance occurred at 12 weeks, with cryotherapy maximum clearance occurred at 8 weeks.

Persistence of warts in imiquimod group and cryotherapy group were same.

**Discussion on clearance rates of warts in imiquimod group:** In our study clearance of warts at 4 weeks was 0%, at 8 weeks was 26.3%, at 12 weeks was 52.6%. So clearance of warts was maximum.

In study conducted by kumar p et al<sup>13</sup> forty-four (34 male and 10 female) patients were randomized to receive imiquimod, 5%, cream and vehicle injection (imiquimod group), and 45 (37 male and 8 female) individuals received vehicle cream and *Mw* vaccine injections (*Mw*group). Three (7%) patients in the imiquimod group and 6 (13%) patients in the *Mw* group withdrew, were lost to follow-up, or defaulted before resolution of the AGWs during the treatment phase.

Of the 44 patients in the imiquimod group, 26 patients (59%) showed complete clearance and 9 (20%) patients each had 75% or more to less than 100% resolution and less than 75% resolution to no response or worsening, respectively. Of the 45 patients in the *Mw* group, 30 patients (67%) showed 100% resolution, 7 patients (16%) had 75% or more but less than 100% resolution, and 8 patients (18%) had less than 75% resolution to no response or worsening.

The mean resolution of AGWs in the imiquimod group was 85%; resolution in the *Mw* group was 83%. The initial clearance was faster in the imiquimod group compared with the *Mw* group, although there was no significant difference in the final out come and adverse effect profile.

In present study complete clearance of warts was 78.9% which is little higher than above study.

In a study conducted by Edwards et al., Beutner et al.<sup>14</sup> clearance rates with imiquimod was 50 to 52%. In present study clearance rates with imiquimod were higher than these studies, not correlating with these studies.

A study on the use of imiquimod for the treatment of genital molluscum contagiosum and genital warts in female patient. Baseline warts cleared from 7 out of 14 (50%) a-c and genital MC lesions cleared from 27 of 36 (75%).<sup>5</sup> Present study clearance rates in imiquimod group were 78.9% which were higher than above study, not correlating with the above study.

In a study conducted by Garland SM et al<sup>15</sup>, an open-label phase ii pilot study investigating the optimal duration of imiquimod 5% cream for the treatment of external genital warts in women. A total of 120 women with a history of genital warts for a median of 3–6 months and prior alternative treatments in 73% were evaluated for total clearance rates. There was no statistically significant difference in complete clearance rates after 16-week follow-up across treatment groups: Four weeks (40.0%), 8 weeks (48.4%), 12 weeks (39.3%), and 16 weeks (51.6%).

In present study clearance of warts at 4 weeks is 0%, at 8 weeks is 26.3%, at 12 weeks is 52.6%. so clearance of warts is maximum. Which are not correlating with the above mentioned study.

**Clearance of warts with cryotherapy:** In present study clearance rates in cryotherapy group at 4 weeks 26.3%, at 8 weeks was 52.6%. Total clearance was 78.9%.

In a study conducted by M Azizjalali et al<sup>16</sup> CO<sub>2</sub> laser therapy versus cryotherapy in treatment of genital warts; a Randomized Controlled Trial (RCT) showed basic characteristic of the lesions in the two groups. In CO<sub>2</sub> laser group, 76 lesions (95%) and in cryotherapy group, 37 lesions

(46.2%) were completely eradicated respectively.

The observed difference was statistically significant, ( $p < 0.001$ ). In cryotherapy group, second and third treatment were needed for complete treatment in 12% and 12.2% of lesions, respectively, while in CO<sub>2</sub> laser therapy, all lesions showed clearance after a single treatment.

In the present study clearance rates in cryotherapy group were totally 78.9%, in the above mentioned study clearance rates were 46.2%. So our study clearance rates in cryotherapy group were higher than above mentioned study, not correlating with the above mentioned study.

In a study conducted by Scheinfeld and Lehman et al<sup>9</sup> clearance of warts with cryotherapy were 79–88%. Our study results were 78.9% which were correlating with this study.

#### Adverse reactions

In a study conducted by Puri N et al<sup>5</sup> the commonest side effect observed in their study was erythema and crusting. In that study, there were no systemic reactions, although local skin reactions (generally of mild or moderate severity) were common. Local reactions caused two patients to discontinue treatment. The most frequently reported local skin reactions were erythema seen in 24% patients, excoriation in 16% patients, itching was seen in 12% patients, erosions were seen in 10% patients, excoriation was seen in 6% patients and pain was seen in 4% patients.

The local reactions noted with imiquimod are most likely due to cytokine-induced inflammation and/or an immune response. Local reactions, which were predominantly of mild and moderate severity, required the discontinuation of treatment in only two patients.

In preclinical trials, the cumulative rate of irritation produced by 5% imiquimod cream was less than that produced by Vaseline Intensive Care Lotion, indicating that imiquimod is not inherently irritating to normal skin.

In this clinical study, there was a significant correlation between the clearance of warts and MC and erythema. An inflammatory response was not required to achieve clearance of the warts; however, patients with such a response were more likely to have wart clearance.

In present study we noticed adverse reactions in imiquimod group in 10.5% of patients. we noticed adverse reactions like, pain, mild erythema erosions. These findings are correlating with the above mentioned study.

In a study conducted by Garland SM et al<sup>15</sup>, An open-label phase ii pilot study investigating the optimal duration of imiquimod 5% cream for the treatment of external genital warts in women Imiquimod was well tolerated, and in those treated for 4 weeks, there was a lower incidence of local skin reactions such as erythema and erosion, and no incidences of pain.

In a study conducted by Buetner et al<sup>14</sup> Imiquimod-treated patients experienced a significantly greater number of local inflammatory reactions than the placebo group. Symptoms and signs associated with the local inflammatory reactions included itching (54.2%), erythema (33.3%), burning (31.3%), irritation (16.7%), tenderness (12.5%), ulceration (10.4%), erosion(10.4%), and pain (8.3%) In present study

adverse reactions with imiquimod are seen in 10.5 % of patients. Which are not correlating with the above study.

In a study conducted by M Azizjalali et al<sup>16</sup> CO<sub>2</sub> laser therapy versus cryotherapy in treatment of genital warts; a Randomized Controlled Trial (RCT): Cryotherapy is an inexpensive, easy applicable method with rapid destructive effect and no serious systemic side effects that make it a safe therapy in pregnancy.

Although, it has some limitations such as risk of vaginal perforation in case of using liquid nitrogen, recurrence in lesions larger than the cryoprobe and some local side effects including blistering and local necrosis.

However, hypopigmentation and scar formation are reported rarely Healing usually occurs in 1-2 weeks time after cryotherapy, although sometimes complete healing may take more than 2 weeks. Blistering developed in 2 lesions of cryotherapy group ( $p = 0.99$ ) and non of cases in laser group. Four lesions recurred in CO<sub>2</sub> laser therapy group (2.5%) and 7 lesions in cryotherapy group (18%) Blistering developed in 2 lesions of cryotherapy group ( $p = 0.99$ ) and non of cases in laser group. Four lesions recurred in CO<sub>2</sub> laser therapy group (2.5%) and 7 lesions in cryotherapy group (18%).

In present study in cryotherapy group we noticed adverse reactions in 10 % of patients ie in two patients, adverse reactions we noticed are local blistering & necrosis which were healed in two weeks with topical antibiotic cream application. These findings are correlating with the above mentioned study. Hypopigmentation, scarring are not noticed in our study.

**Recurrence rates:** Recurrence was observed in 10% cases of cryotherapy, there were no recurrence reported in imiquimod group in the present study.

In a study conducted by puri n et al,<sup>5</sup> they did not notice any recurrences with imiquimod, which is correlating with our study. correlating with the above mentioned study.

In a study conducted Beutner et<sup>14</sup> al recurrence rates were 19%, which are not correlating with present study.

**Recurrence rates with cryotherapy:** Recurrence in a study conducted by M Azizjalali et al<sup>16</sup> showed recurrence rate of 25-39% when genital warts removed by cryotherapy and 60 to 77% when treated by CO<sub>2</sub> laser. However, given the result of our study, treating with CO<sub>2</sub> laser is associated with less recurrence rate than cryotherapy (0.05% against 0.18%). In our study in cryotherapy group recurrence rates are 10%, which are very less correlating with the present study

#### CONCLUSION

Clearance of warts with Imiquimod takes long time when compared to cryotherapy. But it has an advantage of very low recurrence rate, pain less procedure, easily can be applied at home, no technical skills needed, no wastage of time & money for visiting hospital: but patients compliance plays important role in this mode of therapy, as patient needs to apply the cream at home, weekly thrice. Other disadvantages with this is high cost of the drug.

Cryotherapy with liquid nitrogen is a cumbersome procedure, disadvantages are, liquid nitrogen is not easily available in

the market, we have to get that liquid nitrogen from special centres, chemical stores, it requires a special container for its storage even that container costs high.

Cryogun is special tool used to spray the liquid nitrogen, skilled physician required for its application, technique of freeze thaw, need to get followed for every case. Advantages are early clearance of warts, less number of visits to hospital. According to present study there was a significantly higher and early clearance rate with cryotherapy.

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