Comparative Study of Efficacy of Podophyllin Vs 5% Imiquimod in the Treatment of Genital Warts

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ABSTRACT

Introduction: Although genital warts have been documented since the time of Hippocrates, they still remain one of the commonest STDs. This is because the majority are subclinical and no modality of treatment necessarily eradicates warts, maintains clearance, and eliminates the virus. Study was done to evaluate the patients with genital warts, to compare the efficacy of podophyllin, 5% imiquimod, 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 20 months from January 2015 to august 2016.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 podophyllin $p < 0.05$. There was no significant difference in occurrence of adverse reaction in either of treatment groups statistically ($p > 0.05$).Recurrence was observed in 11.15% cases of podophyllin and there were no recurrence reported in imiquimod group in the present study.

Conclusion: According to present study there was a significantly higher and early clearance rate with podophyllin. Clearance of warts with Imiquimod takes long time when compared to podophyllin. Occurance of adverse reactions is almost equal in two groups.recurrence reported in podophyllin but not in IMIQUIMOD group.

Keywords: Podophyllin, Imiquimod, Treatment of Genital Warts

INTRODUCTION

Warts refer to the pedunculated, papular, or macular lesions of the analor genital mucosa and its adjoining area caused by Human papillloma virus infection. Although genital warts have been documented since the time of Hippocrates, they still remain one of the commonest STDs.[1] This is because the majority are subclinical[2] and no modality of treatment necessarily eradicates warts, maintains clearance, and eliminates the virus.[3] The primary reason for treating genital warts is the amelioration of symptoms and ultimately, removal of the warts. In most patients, treatment can induce wart-free periods. If left untreated, visible genital warts can resolve on their own, remain unchanged, or increase in size or number. The method of treatment of genital warts is dependent on available resources, the preference of the patient, and the experience of the health-care provider. There is no definitive evidence suggesting that any of the available treatments is superior to any other and no single treatment is ideal for all patients or all warts. Because of uncertainty regarding the effect of treatment on future transmission of HPV and the possibility of spontaneous resolution, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. In general, warts located on moist surfaces or in intertriginous areas respond best to topical treatment. The treatment modality should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. Most genital warts respond within 3 months of therapy. The response to treatment and any side effects should be evaluated throughout the course of therapy.

This was a interventional study, to compare the efficacy of Podophyllin vs 5% Imiquimod in the treatment of genital warts in 40 patients attending DVL OPD at osmania general hospital for a period of 20 months i.e from Janaury 2015-August 2016.

Study was done to evaluate the patients with genital warts, to compare the efficacy of podophyllin, 5% imiquimod, 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 the duration of 20 months from January 2015 to August 2016. Sample size was total 40 patients, 20 in each group.

Inclusion criteria

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Clearence rate	Podophyllin		Imiquimod	
	Number	%	Number	%
4 weeks	3	16.7	0	0
8 weeks	9	50	5	26.3
12 weeks	0	0	10	52.6
No clearance in 12 wks	6	33.3	4	21.1
Total	18	100	19	100
	Chi square	26.7	P value	<0.001

Table-1: Comparison between clearance and treatment given

Adverse Reaction	Podophyllin		Imiquimod	
	Number	%	Number	%
Present	2	11.1	2	10.5
Absent	16	88.9	17	89.5
Total	18	100	19	100
Chi square		0.012	P value	0.99

Table-2: Relation between adverse reaction and treatment given

Recurrence	Podophyllin		Imiquimod	
	Number	%	Number	%
Present	2	11.1	0	0
Absent	16	88.9	19	100
Total	18	100	19	100
Chi square		2.17	P value	0.338

Table-3: Relation between recurrences and treatment given

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

Exclusion criteria

a. Pregnant and nursing women
b. Patients with HIV seropositiity
c. Patients who were unable to return for follow up visits or comply with the protocol.

Method of collection of data

After taking informed consent all the patients included in the study after clinical diagnosis 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 was calculated for assessing response. Biopsy of the lesions was done to confirm the diagnosis wherever required**.**

Patients were randomly divided into two groups of 20 each. One group was named 1 that receivedpodophyllin and another group was named 2 that received 5%imiquimod. Lesions are photographed with permission before starting the procedure.The therapy was continued until the lesions clear or completion of 12 weeks of treatment 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 podophyllin: It was used in a concentration of 10%–25% dissolved in tincture of benzoin (the usual form used worldwide), mineral oil, linseed oil, rectified spirit,liquid paraffin, or propylene glycol.

We applied Podophyllin to the warts by using a cotton tipped swab once a week. First we have to clean the area with normal saline or distilled water, allow it to dry.

Applications are limited to less than 0.5 ml or 10 cm^2 per treatment session. The surrounding skin is protected with Vaseline, powder, or both. One to 4 h after application, it is completely washed off. This procedure is repeated every week, any adverse reactions are there, they were noted down. post treatment photographs were taken we followed up the patients till 12 weeks. Podophyllin is contraindicated in pregnancy as it can lead to fetal death and abortions.

Procedure of application of imiquimod: written informed consent before was taken before enrolment in the study. Patients were advised to rub the study cream into clean, dry, lesional skin until it disappeared and washed the area with soap and water 8±2 hour after application,everyday before bedtime. In our study, we trained the patients in the method of application of imiquimod in the fisrt episode of application and 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.

RESULTS

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

The analysis of the data obtained was done using SPSS version 17.0. Continuous variables were expressed as mean±SD values. Appropriate statistical tests were used to compare efficacy of podophyllin, 5% imiquimod. 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.

In the present study 3 patients who did not turn up for follow up were excluded from statistical analysis. On comparison of clearance weeks and the treatment given it was observed that 16.7% patients treated with podophyllin achieved clearance at 4 week compared to0% treated with imiquimod. 50% patients% treated with podophyllin achieved clearance at 8 weeks compared to 26.3% treated with imiquimod. 52.6% patients treated with imiquimod achieved clearance at 12 weeks compared to 0% patients treatedwith phodphyllin.

33.3% patients treated with podophyllin achieved incomplete clearance even at 12 week comaperd to 21.1% patients treated with imiquimod. There was a significantly higher and early clearance rate with podophyllin p <0.05 (table-1).
Adverse reactions were 11.1% in podophyllin treated group compared to 10.5% in imiquimod group. There was no significant difference in occurrence of adverse reaction in either of treatment groups statistically (p >0.05) (table-2).
Recurrence was observed in 11.15 cases of podophyllin and 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-3).

DISCUSSION

The present study was conducted in the Department of DVL (Dermatology venereology and 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 divided randomly into two groups of 20 patients each. Group 1 received podophyllin, group 2 received 5% imiquimod.

Clearance rates of warts: In present study clearance rates of warts in podophyllin group are16.7% at 4weeks, 50% at 8 weeks, totally clearance with podophyllin is 66.7%. In imiquimod group are 0% at 4weeks, 26.3% at 8 weeks, 52.6% at 12 weeks, totally clearance with imiquimod is 78.9 Persistence of lesions at the end of 12 weeks with podophyllin is 33.3%, with imiquimod is 21.1%.
According to present study there is no much difference in clearance of warts in between two groups; in podophyllin group clearance of warts occurred early compared to imiquimod group as imiquimod is a immunomodulator.
In a study conducted by Gabriel and Thin[4], 32% was the overall clearance rate observed at 3 months in 60 patients using podophyllin and podophyllin with TCA in two groups of patients.
In present study over all clearance rate is 66.7%. Our clearance rates are not correlating with this study. Application of the medicine by the same observer, possibly early presentation of the disease, regular attendance of the patients and presence of only a few warts in many patients (less than 5 in 40% cases) could be reasons for the high clearance rate in the present study.
In a study conducted by Raj gopal et al,[5] topical podophyllin and podophyllotoxin for treatments of genital warts were compared.[5] The efficacy of podophllin and podophyllotoxin was compared in the treatment of genital warts in 72 men. Group A consisting of 35 patients were treated with podophyllin in tincture benzoin compound at weekly intervals while 37 men in Group B were advised to apply 0.5% podophyllotoxin solution twice a day for three consecutive days every week.
After 6 weeks, 33(89.1%) of podophyllotoxin group and 29 (82.8%) men of podophyllin group were completely cured. In present study clearance rates in podophyllin group are 66.7%which are slightly less than the above mentioned study.
Discussion on clearance rates of warts in imiquimod group
In a study conducted by Beutner et al.[6] clearance rates with imiquimod is 50 to 52%. In our 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.In present study clearance rates with imiquimod are higher than these studies, not correlating with the above study.
In a conducted by Puri N et al[7] 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%). Present study clearance rates in imiquimod group are 78.9%which is higher than above study, not correlating with the above study.
In a study conducted by Garland SM et al, an open-label phase, pilot study investigating the optimal duration of imiquimod 5% cream for the treatment of external genital warts inwomen.[8] A total of 120 female patients with a history of genital warts for a median of 3–6 months, were evaluated for total clearance rates. There was no significant difference in complete clearance rates statistically after 16-week follow-up across treatment groups.

Adverse reactions

In a study conducted by Puri N et al[7] on the use of imiquimod for the treatment of genital molluscum contagiosum and genital warts in female patients. Erythema seen in 24% patients was the most frequently reported local skin reaction followed by excoriation seen in 16% patients, itching was seen in 12% patients, excoriation in 6% patients, erosions in 10% patients, and pain was seen in 4% patients.
The adverse local reactions noted with imiquimod are likely due to cytokine-induced inflammation and/or an immune response. Only two patients discontinued the treatment due to local reactions, which were predominantly of mild and moderate severity. Imiquimod is not inherently irritating to normal skin.It is supported by preclinical trials showing the cumulative rate of irritation produced by 5% imiquimod cream was less than that produced by Vaseline Intensive Care Lotion.
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 imquimod 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 Buetner et al.[9] 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.

Recurrence Rates: Recurrence was observed in 11.1% cases of podophyllin and there were no recurrence reported in imiquimod group in the present study.

In a study conducted by Raj gopal et al[5] by topical podophyllin and podophyllotoxin for treatments of genital warts, 8 (28.5%) men in Group A and 11 (32.3%) in Group B showed some evidence of recurrence of warts after 6 months. In present study recurrence of warts in podophyllin group seen in11.1% which were less than above mentioned study, may be attributed to lesser time of follow up in our study.

In present study in imiquimod group we did not notice any recurrences. In a study conducted by Puri N et al[7] on the use of imiquimod for the treatment of genital molluscum contagiosum and genital warts in female patient, they did not notice any recurrences with imiquimod, which is correlating with our study.

In study conducted by Kumar P et al[10] there was no recurrence of AGWs in patients with complete clearance at the 3-month follow-up and no serious adverse events. Our study is correlating with this study also in the aspect of occurance of recurrence warts with imiquimod.

In a study conducted by Beutne[11] et al recurrence rates were 19%, which are not correlating with present study.

CONCLUSION

Four traditional goals for the treatment of sexually transmitted infections (STIs), i.e. eradication of infection, elimination of symptoms, prevention of long-term
sequelae and interruption of transmission are hard to achieve with AGWs.

In order to completely clear the infection, one would need to eliminate the bulk of the
visible disease as well as the subclinical infection in basal cell of the epidermis/epithelium where HPV persist in a form of episomes.

Occurance of adverse reactions is almost equal in two groups. With Podophyllin early clearance of warts occurs. but it has a disadvantage of recurrence. It is a physician applied out patient procedure. In this mode also paient compliance plays a vital role as they have to come to hospital every week. Advantages are cost effective, simple procedure.

Clearance of warts with Imiquimod takes long time when compared to podophyllin. But it has an advantage of very low recurrence rate, pain less procedure, easily can be applied at home, no technical skiils needed, no wastage of time and 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.

According to present study there was a significantly higher and early clearance rate with podophyllin.

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