ORIGINAL ARTICLE

Imiquimod vs cryotherapy in the treatment of anogenital warts

Lubna Khondker, MD

Associate Professor, Dept of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

ABSTRACT

Introduction: Anogenital warts are one of the most common sexually transmitted diseases worldwide. In recent times, anogenital warts have emerged as a disease of major public concern because of its high prevalence, sexual mode of transmission, its association with various neoplasia and HIV, difficulty in treatment and high rates of recurrence.

Objective: The aim of this study was to compare Imiquimod vs cryotherapy in the treatment of anogenital warts.

Materials and Methods: A randomized controlled clinical trial was conducted from April 2019 to March 2020 in the Department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Primarily, 64 patients were enrolled in this study and randomized by lottery method into group A and Group B and patients of group A was treated with Imiquimod and patients of group B was treated with cryotherapy.

Results: In this study of 64 patients mean age of Group A patients were 25.9±12.6 years and Group B patients were 26.4±12.4 years. Regarding efficacy, excellent 19(59.4%), significant 8(25.0%), moderate 3(9.4%), mild (3.1%) and no response 1(3.1%) was found in Group A and excellent outcome 13(40.6%), significant 3(9.4%), moderate 9(28.1%), mild 7(21.9%) in Group B and Overall excellent to significant outcome was 27(84.4%) in Group A and 16(50.0%) in Group B (p=0.018). On the basis of side effects, only hyperpigmentation (12.5%) was observed in group A and skin atrophy (31.3%), dyspigmentation (15.6%) and hypopigmentation (12.5%) were found in group B. Regarding recurrence of warts, significantly higher percentage of recurrence was found in group B in comparison to group A (12.5% in group A and 34.4% in patients in group B).

Conclusion: Imiquimod is more effective and safer than cryotherapy in the treatment of anogenital warts.

KEY WORDS: Anogenital warts, Imiquimod, Cryotherapy

INTRODUCTION

Anogenital warts (external genital warts), the most common sexually transmitted viral disease of genitalia is caused by Human Papilloma Virus (HPV).[1] The worldwide prevalence of infection with Human Papilloma Virus (HPV) in women without cervical abnormalities is 11-12%.[2] Approximately 1% of the sexually active population has symptomatic genital warts.[3] Anogenital warts are sexually transmitted; with transmission rates of 60%, but materno-fetal transmission may also occur.[4] Genital warts usually caused by human papillomavirus genotypes 6 or 11.[1]

The spectrum of disease varies from subclinical infection to active disease.[5] HPV virions stimulate the proliferation of keratinocytes in the basal layer of the epithelium which along with viral replication results in exophytic growth.[1] The anogenital warts may enlarge enormously during pregnancy and can obstruct the normal labour.[5] There is 12.2% risk of vertical transmission of HPV to a neonate delivered by normal vaginal

Correspondence: *Dr. Lubna Khondker, Associate Professor, Dept of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Email: lubnaderma@gmail.com*

route.[6,7] The treatment of EGW poses a therapeutic challenge. If not treated, they may resolve spontaneously, increase in size or number or remain unchanged depending upon the patient's immunological status.[8] Currently, treatment of genital warts focuses on removal of warty tissues, rather than eradicating the virus.[9-12] A wide range of therapeutic options are available for treatment of EGW like cytotoxic agents (Trichloroacetic acid, Phenol, Podophyllin, 5-Fluorouracil, Retinoids and Bleomycin), physical ablation (Electrical destruction and Cryotherapy) and immunomodulation (Imiquimod, Interferon, purified protein derivative and the HPV vaccine).[1] A large armamentarium of therapies is available for EGWs, but no definitive therapy has emerged as the ideal standard of care.[13] Although effective to some extent, have high recurrence rates, and require long-term or repeat treatment.[12,14]

Cryotherapy destroy tissue by thermal necrosis of HPV infected keratinocytes in four stages: (i) rapid heat transfer; (ii) tissue injury; (iii) vascular stasis and occlusion; and (iv) local inflammation conducive to the development of an effective cell-mediated response.[15] It is the most recommended line of therapy for EGW except in cases of blood dyscrasias, Cold Intolerance, Raynaud's disease, Cold urticaria, Cryoglobulinaemia, Pyoderma gangrenosum and autoimmune diseases.[1] The immediate side effects are pain, blistering and ulcer besides the late complications of scarring, hypopigmentation and hyperpigmentation, particularly in black skin.[15] This treatment can also be expensive, as a number of outpatient visits may be required for a satisfactory result.[2] Imiquimod an immune modulator, is a choice for home treatment of genital wart.[5] The 5% Imiquimod cream was first approved by the FDA in the late 1990s for the immunotherapeutic treatment of external anogenital warts.[16,17] Imiquimod directly activates innate immune cells and subsequent adaptive immune responses through activation of Toll-like receptor 7 (TLR-7).[18,19] Imiquimod facilitates antigen-specific CD8+ T-cell accumulation in the genital tract, and resulting in tumour growth inhibition through IFN γ.[20] Imiquimod also has the ability to induce apoptosis of viral infected cells and tumour cells.[21-23] Imiquimod is generally well tolerated. The most common local inflammatory reaction reported in one study was erythema and recurrence occurred as late complication.[24]

The major reason for treatment failure of EGW is the anatomically difficult to approach locations of the lesions, pain sensitivity of the area to be treated, the resilience of the virus and the residual subclinical infection. The subclinical infection persists because HPV DNA continues to reside in the margins just outside the treatment area.[25] High rates of recurrence are noted in promiscuous, pregnant and immunocompromised patients. Since all available treatment modalities have shortcomings, various combination therapies are being employed in treating EGW.[26] The present study was undertaken to evaluate the synergistic effect of Imiquimod as a chemotherapeutic adjunct to an ablative therapy of liquid nitrogen cryotherapy versus liquid nitrogen cryotherapy alone in the treatment of EGW.

MATERIALS AND METHODS

A randomized controlled clinical trial was conducted from April 2019 to March 2020 in the Department of Dermatology and Venereology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Primarily 64

patients were enrolled in this study and randomized by lottery method into group A and Group B and each group comprised of 32 patients. Patients of group A were treated with Imiquimod. Healthy men and women aged 18 years or older participated in this trial. Patients had a diagnosis of anogenital warts, with a minimum of 2 and a maximum of 50 external lesions. Patients were enrolled only when judged to be healthy after a medical history taking, physical examination, and laboratory testing yielded no significant positive or abnormal findings. Patients' immunosuppressed by virtue of disease or use of medication were excluded, as were pregnant or lactating women, and women not using contraception. Patients with current chemical or alcohol dependency were not enrolled. Patients could not have treated their warts within 4 weeks before enrollment, and the skin must have returned to normal following any previous therapy. Patients with skin disease in the area to be treated, including frequently recurrent herpes simplex virus infection, were excluded. Patients having used any local medications for any purpose, including topical corticosteroids, in the target area during the 2 weeks prior to enrollment were excluded.

At the initiation visit, anogenital warts were measured and patients were instructed carefully about the use of the test medication and they were asked to maintain diaries to record dosing and to ensure compliance. The medication was to be used 3 times each week until all baseline warts were confirmed to have disappeared or for 16 weeks, whichever occurred first. Medication was to be applied every other day for 3 doses per week with individual applications separated by no less than 36 hours and no more than 96 hours. After the third dose, there was a 2-day pause (60-120 hours) before the next week's dosing. No other topical preparations of any kind were allowed during the treatment period.

They were told first to clean and dry the area. They were then to apply test cream to all external lesions in an amount that could be rubbed in until the cream disappeared. They were instructed to allow the cream during their normal sleeping time. The test medication was to be washed off with soap and water after an allowable application time of 6 to 10 hours. At any time during the treatment phase that warts were no longer visible, use of the test cream was stopped and the patient was entered into the follow-up phase of the study to investigate recurrence. Patients whose warts did not disappear during the 16-week treatment phase did not enter the follow-up phase.

During the treatment phase of the trial, patients were seen weekly for 2 weeks and then biweekly until their warts cleared or for the remainder of the 16-week treatment period. At these visits, patient diaries were checked and patients were questioned for the development of adverse reactions. Warts were measured and the area was examined for signs and symptoms of local inflammation.

Patients whose initially identified and treated warts disappeared by 16 weeks were entered, as clearing of the warts occurred, into a 12-week treatment-free follow-up phase. New warts that had appeared during the follow-up phase in these patients could be treated with conventional wart therapy. During this follow-up phase, patients were seen biweekly to evaluate for recurrence of warts. Similar procedures were performed as were done during the treatment phase. Participation in the study was ended at completion of the 12-week follow-up period or on recurrence of a

baseline wart, whichever occurred first.

Patients of group B were treated with cryotherapy (here liquid nitrogen at a temp. of -195.6 °C was used as cryogen) with a spray gun using nozles of suitable sizes appropriate for the patient every 3 weeks interval for a maximum frequency of 4 (four) treatment. The spray gun was held perpendicular to the wart at a distance of 1-2 cm. The wart was sprayed until the ice-ball formation had spread from the centre to include the edge of the wart & a 1 mm margin. A double freeze-thaw was practiced in this study. Post-treatment follow-up was done 4 weekly up to 12 weeks after the end of the last treatment given. Base line evaluation was done at first visit. The size of warts selected for treatment was also be recorded on standardized data collection sheets. Response to treatment was graded as follows-

0= no response

1= mild response (1-25% reduction in size of lesions).

2= moderate response (26-50% reduction in size of lesions).

3= significant response (51-75% reduction in size of lesions).

4= excellent response (76%-100% reduction in size of lesions).

RESULTS

This study was a randomized controlled therapeutic trial that carried out with the aim of comparing the efficacy and safety of Imiquimod vs cryotherapy in the treatment of anogenital warts. In this study 64 patients were selected randomly by lottery and divided into two therapeutic groups, one was experimental (Group A) and another was control (Group B); each group consisted of 32 patients.

Table 1 Age distribution of the study patients (n=64)

Age in years	Group A(n=32)	Group B(n=32)	p value
≤20	12(37.5)	11(34.4)	
21-40	16(50.0)	17(53.1)	
41-60	4(12.5)	4(12.5)	
Total	32(100.0)	32(100.0)	
Mean±SD Range	25.9±12.6 (5-55) years	26.4±12.4 (9-60) years	0.858^{ns}

ns:not significant, n: number of patients, P value has reached from unpaired t-test.

The table 1 shows that mean age of Group 'A' patients were 25.9±12.6 years ranging from 5 to 55 years and Group 'B' patients were 26.4±12.4 years ranging from 9 to 60 years. Analysis reveals that no statistically significant difference between Group 'A' and Group 'B' patients ($p>0.05$). It was found that among Group 'A' patients, highest percentage (50.0%) were from age group 21-40 years, whereas among Group 'B' highest percentage (53.1%) was from age group 21-40 years.

Table 2 Sex distribution of the study patients (n=64)

Sex	Group A(n=32)	Group B(n=32)	p value
Male	7(21.9)	12(37.5)	0.171^{ns}
Female	25(78.1)	20(62.5)	
Total	32(100.0)	32(100.0)	

P value has reached from Chi-square test, ns: not significant, n: number of patients

The table 2 shows that out of 32 patients, 21.9% are male and 78.1% are female in Group 'A'. Among 32 patients in Group B 37.5% were male and the rest 62.5% were female. Analysis reveals statistically no significant difference between

male and female (p>0.05) between two groups.

Table 3 Distribution of two groups by size of warts and duration of warts

	Group A(n=32) Mean±SD	Group B(n=32) Mean±SD	p value
Size of warts (in mm) Largest (range)	6.47±4.68 (1.5- 20.0)	6.44±4.23 (2.0 -20.0)	0.976
Size of warts (in mm) Smallest (range)	0.87±0.49 (0.5-2.0)	1.09±0.58 (0.5-2.0)	0.137
Number of warts	15.31±16.3	11.72±17.83	0.430
Duration of warts in weeks (range)	9.50±5.0 2 (2.0-24.0)	9.41±6.16 (1.0-24.0)	0.947

P value has reached from Unpaired student t-test

The table 3 shows that largest size of warts, in Group 'A'6.47±4.68 and 6.44±4.23 in Group 'B' and total number of warts, in Group 'A' 15.31±16.3 and 11.72±17.83 in Group 'B'. Analysis shows that size of warts, number of warts and duration of warts had no statistically significant difference between two groups (p>0.05).

Table 4 Final outcome (at the end of follow up) between two groups

Final outcome	Group A (n=32)	Group B (n=32)	p value
No response (0%)	1(3.1)	0(0.0)	
Mild(1-25% reduction of size of warts)	1(3.1)	7(21.9)	
Moderate (26-50% reduction of size of warts)	3(9.4)	9(28.1)	0.018[s]
Significant (51-75% reduction of size of warts)	8(25.0)	3(9.4)	
Excellent (76-100% reduction of size of warts)	19(59.4)	13(40.6)	
Total	32(100.0)	32(100.0)	

P value has reached from Chi-square test

Table 4 showing the treatment responses, excellent 19(59.4%), significant 8(25.0%), moderate 3(9.4%), mild (3.1%) and no response 1(3.1%) in Group 'A' and excellent outcome 13(40.6%), significant 3(9.4%), moderate 9(28.1%), mild 7(21.9%) in Group 'B' and Overall excellent to significant outcome is 27(84.4%) in Group 'A'and 16(50.0%) in Group 'B' and Excellent to significant outcome is significantly higher (84.4%) in Group 'A' in comparison to Group 'B' (p=0.018).

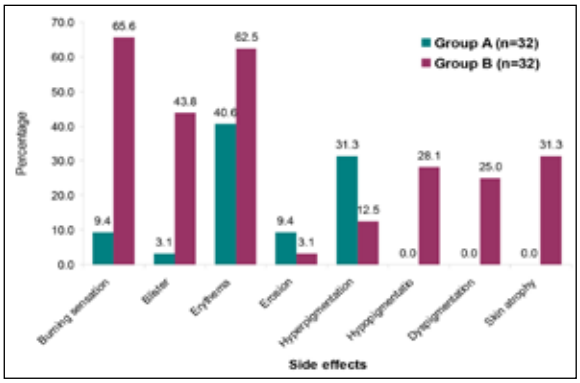

Fig. I Bar diagram showing the side effects of the patients.

Fig. 1 shows that burning sensation, blister, hypopigmentation, dyspigmenation and skin atrophy are significantly higher in group 'B'(cryotherapy group) group compare to group 'A' and erosion and hyperpigmentation is higher in group 'A'. Hypopigmentation, dyspigmentation and skin atrophy are found in group 'B' (cryotherapy group) but are absent in group 'A'. P value has reached from Chi-square test.

Table 5 Distribution of the study by recurrence rate between two groups

Recurrence	Group A(n=32)	Group B(n=32)	p value
Yes	4(12.5)	11(34.4)	0.038[s]
No	28(87.5)	21(65.6)	
Total	32(100.0)	32(100.0)	

P value has reached from Chi-square test, s:significant, n: number of patients

The table 5 shows that recurrence of warts are 12.5% in group 'A' and 34.4% in patients in group 'B' and Significantly higher percentage of recurrence has found in group 'B' in comparison to group 'A'.

Fig. 2 shows that the observed persistent side effects are skin atrophy (31.3%), dyspigmentation (15.6%), hypopigmentation (12.5%), are found in group 'B' (cryotherapy group) but only hyperpigmentation (12.5%) is observed in group 'A'. P value has reached from Chi-square test.

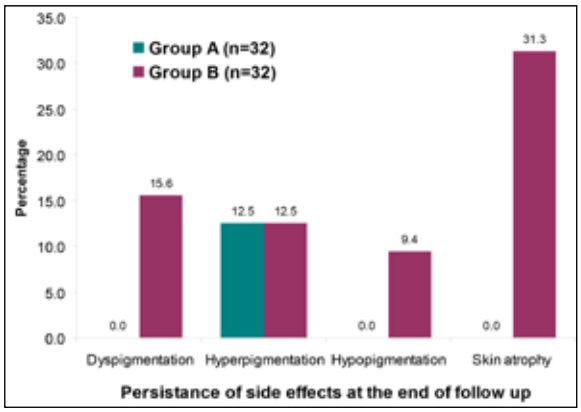

Fig. 2 Bar diagram showing the persistence of side effects.

DISCUSSION

In this study regarding efficacy, excellent 19(59.4%), significant 8(25.0%), moderate 3(9.4%), mild (3.1%) and no response 1(3.1%) was found in Group A and excellent outcome 13(40.6%), significant 3(9.4%), moderate 9(28.1%), mild 7(21.9%) in Group B and Overall excellent to significant outcome was 27(84.4%) in Group A and 16(50.0%) in Group B (p=0.018). Based on treatment outcome, Imiquimod was found more effective than cryotherapy in the treatment of anogenital warts in this study. These findings are not similar with study finding of Stefanaki at al and Mohanlal et al.[27,28] Stefanaki at al conducted a study to compare the efficacy of cryotherapy versus imiquimod 5% in the treatment of anogenital warts. Eighty HIV-negative males were included in the analysis; 35 of them were treated with imiquimod 5% three times a week for 6-10 hours and 45 of them with cryotherapy once in three weeks. Follow-up appointments were arranged every month for the first three months and then at six and 12 months. Treatment for both groups was continued for a total of 12 weeks or until the warts cleared. At the end of three months, irrespective of the type of treatment, 78.8% of the patients demonstrated 100% improvement. Cryotherapy was more effective, as 86.7% of patients showed 100% improvement compared with 68.6% of patients in the imiquimod group. On the contrary, 17.1% of the imiquimod group did not show any signs of improvement, compared with 2.2% of the cryotherapy group (P=0.017). However, patients treated with imiquimod tended to improve earlier than patients on cryotherapy (P=0.012). Cryotherapy was more effective than imiquimod for the treatment of anogenital warts.[27] Probable reason for dissimilarity may be due to the reason that this study includes female group also and female are more sincere in application of imiquimod cream when compared to males. Also, usually the baseline wart area tends to be smaller for women.

Mohanlal et al conducted a study with patients of genital warts attending the department of dermatology and venereology, Osmania general hospital, Hyderabad, India. They compared the efficacy of 5% imiquimod vs cryotherapy in the treatment of genital warts, for a duration of 24 months with total 40 patients, 20 in each group. On comparison of clearance weeks and the treatment given they observed that there was a significantly higher and early clearance rate with cryotherapy ($p < 0.05$) than Imiquimod treated

group.[28] Probable reason for dissimilarity may be due to the reason that this study includes anal area also and efficacy of imiquimod is reported to be more in anal area.

Edwards et al conducted a study with patients of anogenital warts. A total of 311 patients at 11 clinical centers were enrolled in this trial, including 131 women (42%) and 180 men (58%). One hundred nine patients were randomized to receive 5% imiquimod cream, 102 patients to receive 1% imiquimod cream, and 100 patients to receive vehicle cream. Although the baseline wart area tended to be smaller for women in each group than for men, there was no statistically significant difference among treatment groups for either sex (men, P>.50; women, P>.50). Also, the reported duration of the current outbreak of anogenital warts in women in each group was shorter than that of men; the difference in duration of warts among treatment groups for men was statistically significant (P=.01). Median duration of warts in the current outbreak for women was 3.4 months (5% imiquimod group), 3.1 months (1% imiquimod group), and 4.4 months (vehicle group). The reported median duration of warts for men was 6.7 months (5% imiquimod group), 26.4 months (1% imiquimod group), and 7.9 months (vehicle group). Seventy-seven patients discontinued use of medication during the study, and the discontinuation rate was similar for each group. Nineteen patients (17%) in the 5% imiquimod group stopped use of medication, compared with 31 patients (30%) in the 1% imiquimod group and 27 patients (27%) in the vehicle group. Of the 77 patients who withdrew participation in the study, 4 patients discontinued participation because of adverse reactions and 18 patients for lack of therapeutic effect. These patients were classified as treatment failures. The treatment failures included 6 patients (6%) in the 5% imiquimod group, 8 patients (8%) in the 1% imiquimod group, and 8 patients (8%) in the vehicle group. Fifty-five participants did not complete the study because of noncompliance, personal reasons, or unavailability for follow-up. Because these patients were removed for reasons assumed to be unrelated to adverse reactions or lack of efficacy, they were not included in the treatment failures analysis of clearance rates. In this analysis, 13 patients (12%) in the 5% imiquimod group, 23 patients (23%) in the 1% imiquimod group, and 19 patients (19%) in the vehicle group were excluded. The intent-to-treat analysis included all randomized patients. A total of 33 (31%) of 106 patients using 5% imiquimod cream developed new warts (not present at baseline) during the study. This rate compares with 44 (42%) of 97 patients using 1% imiquimod cream and 41% of patients using vehicle cream (P=.20).[29]

Side effects seen in this study included skin atrophy (31.3%), dyspigmentation (15.6%), hypopigmentation (12.5%) in cryotherapy group, and only hyperpigmentation (12.5%) was observed in imiquimod group. Significantly higher percentage of recurrence was found in cryotherapy group in comparison to imiquimod group. The study findings were not similar with mohanlal et al study, they observed that occurence of adverse reactions to be almost equal in two groups (p >0.05). Regarding recurrence in Mohanlal et al, it was observed in 10% cases of cryotherapy group and there were no recurrence reported in imiquimod group.[28] But Stefanaki at al showed that no statistically significant difference regarding the recurrence rate between the two groups

(P = 0.138).[27]

Edwards et al observed that local inflammatory reactions were the most common adverse events but these were generally well tolerated. There was good correlation between the investigators' and the patients' descriptions as to the presence and severity of local inflammation, although patients tended to assess their reactions as less severe. The most common local inflammatory reaction was erythema, occurring, by investigators' judgment, in 71(67.0%) of 106 patients treated with 5% imiquimod cream. The erythema was severe at some point in 6 patients (5.7%) and moderate in 36 patients (34.0%). There was correspondingly less erythema in those treated with 1% imiquimod cream (25 patients, or 25.8%) or vehicle cream (23 patients, or 24.2%), with only 4 and 3 patients, respectively, developing moderate redness and no patients experiencing severe redness. There were no other severe reactions of any kind at any time in more than 1 patient in any group. The 1% imiquimod cream and vehicle cream were both associated with less severe local inflammatory reactions. In addition, less than 25% of these patients experienced any local inflammation. The majority of patients in each of the 3 treatment groups experienced no flaking, erosion, edema, scabbing, induration, vesicles, or ulceration. Only 2 patients (both using 5% imiquimod cream) were excluded from the study by investigators because of local reactions.[29]

CONCLUSION

Imiquimod is more effective and safer than cryotherapy in the treatment of anogenital warts. A prospective multicentre evaluation with a larger sample size and a longer study period with long time follow-up is recommended.

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