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Original Article

Safety profile of imiquimod vs. cryotherapy in the treatment of condylomata acuminata

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Abstract

Introduction In recent times, condylomata acuminata has 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. Imiquimod is effective in the treatment of condylomata acuminata but there is paucity of data regarding its side effect and its comparison with established treatment method-cryotherapy.

Objective The aim of this study was to compare the safety level of Imiquimod vs cryotherapy in the treatment of condylomata acuminata.

Patients 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 Based on side effects of study findings, burning sensation, blister, hypopigmentation, dyspigmenation and skin atrophy were significantly higher in group 'B' (cryotherapy group) compare to group 'A' and erosion and hyperpigmentation were higher in group 'A'. Hypopigmentation, dyspigmentation and skin atrophy are found in group 'B' (cryotherapy group) but are absent in group 'A' (imiquimod group). Regarding persistent side effects, skin atrophy (31.3%), dyspigmentation (15.6%), hypopigmentation (12.5%) were found in cryotherapy group but only hyperpigmentation (12.5%) was observed in imiquimod group and significantly higher percentage of recurrence had found in cryotherapy group in comparison to imiquimod group (12.5% in group A and 34.4% in patients in group B).

Conclusion Based on study results, it can be concluded that Imiquimod is safer than cryotherapy in the treatment of condylomata acuminata.

Key words
Condylomata acuminata, imiquimod, cryotherapy.

Introduction

Condylomata acuminata (anogenital wart, external genital wart) is one of the most common sexually transmitted diseases worldwide, is caused by Human Papilloma Virus (HPV) genotypes 6 or 11.[1,2] Approximately 1% of the sexually active population has symptomatic genital warts.[3] Transmission rates of condylomata acuminata is 60%, but materno-fetal transmission may also occur.[4] HPV virions stimulate the proliferation of keratinocytes in the basal layer of the epithelium which along with viral replication results in exophytic growth.[1] Condylomata

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acuminata may enlarge enormously during pregnancy and can obstruct the normal labour. There is 12.2% risk of vertical transmission of HPV to a neonate delivered by normal vaginal route.[5,6] The treatment of condylomata acuminata 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.[7] Currently, treatment of condylomata acuminata focuses on removal of warty tissues, rather than eradicating the virus.[8,9] A wide range of therapeutic options are available for treatment 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).[10] A large armamentarium of therapies is available, but no definitive therapy has emerged as the ideal standard of care in the treatment of condylomata acuminata.[11] Although effective to some extent, have high recurrence rates and require long-term or repeat treatment.[12]

Cryotherapy destroys tissue by thermal necrosis of HPV infected keratinocytes but the immediate side effects are pain, blistering and ulcer besides the late complications of scarring, hypopigmentation and hyperpigmentation, particularly in black skin.[13] 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.[14] Imiquimod directly activates innate immune cells and subsequent adaptive immune responses through activation of Toll-like receptor 7 (TLR-7). Imiquimod facilitates antigen-specific CD8+ T-cell accumulation in the genital tract, and resulting in tumour growth inhibition through IFN γ. Imiquimod also has the ability to induce apoptosis of viral infected cells and tumour cells.[15]

Although regarded as a safe drug, mild-to-moderate, local and systemic, adverse effects of imiquimod may occasionally occur.[16] Since vitiligo-like hypopigmentation associated with imiquimod treatment of condylomata acuminata was first reported by Brown in 2005, to the best of our knowledge there have been only eight patients with either vitiligo or vitiligo-like hypopigmentation associated with imiquimod treatment of condylomata acuminata described in the literature.[17-22] Imiquimod not only kills the HPV but also destroys melanocytes. Similarly, the mechanism of imiquimod-induced vitiligo may be that the medication activates the Langerhans cells in the lesions via antigen presentation, leading to the destruction and apoptosis of the melanocytes. Imiquimod-induced apoptosis of melanocytes was confirmed by TUNEL assay, Hoechst 33258 staining, and measuring mitochondrial membrane potential in melanocytes.[23] Moreover, imiquimod can induce cytokines such as IFN-α, TNF-α, IL-6, IL-8, and nitric oxide to cause vitiligo.[24] Additionally, imiquimod binds to Toll-like receptor-7 and −8, increasing production of proinflammatory cytokines such as IFN-α, TNF-α, and LI-12, which play a role in the pathogenesis of vitiligo.[25] The present study was undertaken to evaluate adverse effect of Imiquimod to cryotherapy in the treatment of condylomata acuminata.

Patients 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, condylomata acuminata /anogenital warts were measured and patients were instructed carefully in 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 was 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 5 (five) 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.

Results

This study was a randomized controlled therapeutic trial that carried out with the aim of comparing the safety profile of Imiquimod vs. cryotherapy in the treatment of condylomata acuminata. 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 was consisted of 32 patients.

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 mean age difference between Group 'A' and Group 'B' patients ($p>0.05$). It is found that among Group 'A' patients, highest percentage (50.0%) has age group 21-40 years, whereas among Group 'B' highest percentage (53.1%) has age group 21-40 years.

The side effects of the patients at the end of 16 week treatment period was shown in **Figure 1**. 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'.

Table 1 Age distribution of the study patients.

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	25.9±12.6	26.4±12.4	0.858ns
Range	(5-55) years	(9-60) years	

ns: not significant, n: number of patients, P value has reached from unpaired t-test.
Group A: Imiquimod and Group B: Cryotherapy

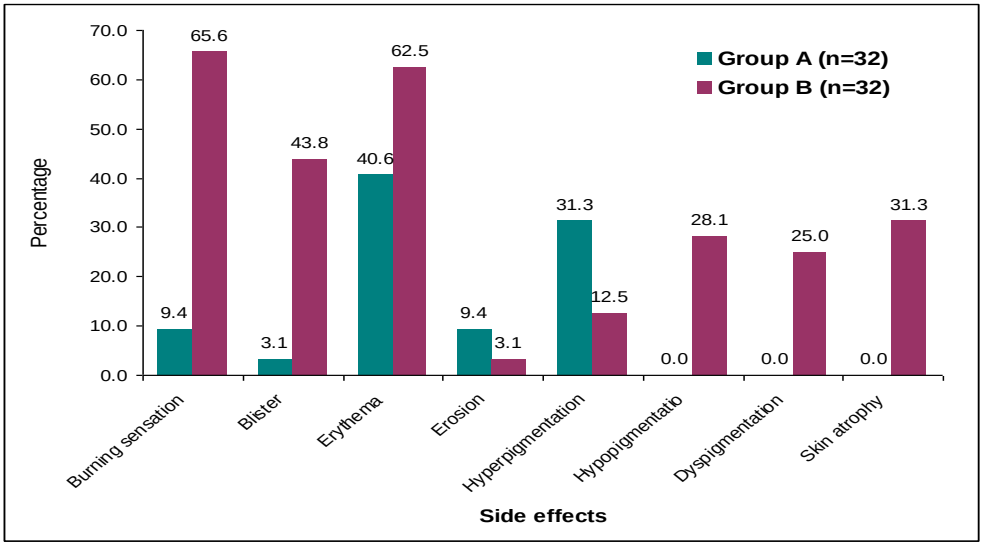

Figure 1 Side effects of the patients at the end of 16 week treatment period.

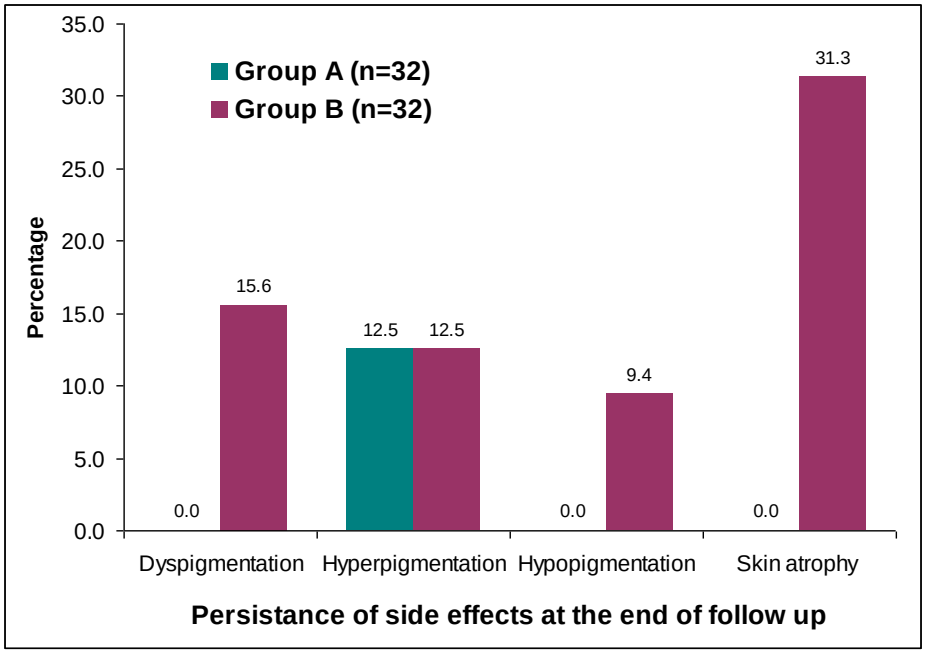

Figure 2 Persistence of side effects at the end of 12 week follow up period.
Group A: Imiquimod and Group B: Cryotherapy

Table 2 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)	0.038s
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
Group A: Imiquimod and Group B: Cryotherapy

Figure 2 shows the persistence of side effects at the end of 12 week follow up period. 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'.

Table 2 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' than group 'A'.

Discussion

Based on side effects of this study findings at the end of 16 week treatment period, burning sensation, blister, hypopigmentation, dyspigmenation and skin atrophy were significantly higher in group 'B'(cryotherapy group) compare to group 'A' and erosion and hyperpigmentation were higher in group 'A'. Hypopigmentation, dyspigmentation and skin atrophy are found in group 'B' (cryotherapy group) but are absent in group 'A' (imiquimod group). Regarding persistent side effects at the end of 12 week follow up period, skin atrophy (31.3%), dyspigmentation (15.6%), hypopigmentation (12.5%) were found in cryotherapy group but only hyperpigmentation (12.5%) was observed in imiquimod group and significantly higher percentage of recurrence had found in cryotherapy group in comparison to imiquimod group (12.5% in group A and 34.4% in patients in group B). My study findings were not similar with Mohanlal *et al.* study, they observed that occurance of adverse reactions is almost equal in two groups ($p > 0.05$). Regarding recurrence, Mohanlal *et al.* was observed in 10% cases of cryotherapy group and there were no recurrence reported in imiquimod group in their

study.[26] But Stefanaki at al showed that no statistically significant difference regarding the recurrence rate between the two groups (P=0.138).[25]

Yang LJ conducted a study with 46 pregnant women with CA, treated with cryotherapy combined with PCs. All patients were followed up at 1 and 3 months. At the 1-month follow-up, only 1 case of recurrence was identified. At 3 months, 5 cases of recurrence were identified, and the recurrence rate was 10.9%. All patients reported no discomfort, with the exception of mild-to-moderate pain. In some patients, various degrees of edema and erythema accompanied by mild-to-moderate burning pain occurred around the treatment area. Blisters in the treated area ruptured in 4 patients and the ruptured tissues healed within 4 days. No depigmentation or scar formation was observed, and no patients reported any severe adverse events.[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.[28]

Wenfei *et al.* presented a 28-year-old Chinese male in their clinic with a 3-year history of condylomata acuminata of the penis. He was advised to use imiquimod 5% cream. After about 12 weeks of continuous use, he again presented to the clinic complaining of vitiligo-like depigmentation of the macules on his penis. He was instructed to stop using the imiquimod, but the macules in the treated areas gradually enlarged and asymptomatically merged. Physical examination showed vitiligo patches involving the glans penis, the shaft of the penis, and the scrotum, along with some remaining pigmented areas within the vitiligo plaques. Wood's light accentuated the depigmented areas. A skin biopsy was performed on the dorsal surface of the penis, which showed a complete absence of melanocytes and melanin granules in the basal layer. He was diagnosed, clinically and pathologically, with imiquimod-induced localized vitiligo.[1]

Beutner *et al.* conducted a prospective, multicenter, double-blind, randomized, vehicle-controlled trial to evaluate the safety of patient-applied imiquimod for up to 16 weeks for the treatment of external genital warts. Wart recurrence was investigated during a 12-week treatment-free follow-up period. For subjects who completed the follow-up period, recurrence rates after a complete response were 19% (9 of 48 patients) in the 5% imiquimod cream group,

17% (2 of 12) in the 1% imiquimod cream group, and 0% (0 of 3) in the vehicle-treated group. Of the 11 patients who experienced a recurrence during the follow-up period, three of these recurrences were noted at week 4, four were noted at week 6, two were noted at week 8, one was noted at week 10, and one was noted at week 12 of follow-up. The most common local skin reactions in all treatment groups were erythema, excoriation or flaking, and erosion. For the 5% imiquimod cream group, erythema was reported as mild for 16.3% of the patients, moderate for 43.5% of the patients, and severe for 22.8% of the patients. For the 1% imiquimod cream group, 34.9% of the patients reported mild erythema, 16.3% reported moderate erythema, and 9.3% reported severe erythema. None of the vehicle-treated patients had severe erythema; only 8.7% had moderate erythema, 28.3% had mild erythema, and 63.0% had no erythema. In the 5% imiquimod cream group there was a relationship between the complete clearance of warts and erythema at the wart site (assessed by using the highest level of erythema noted by either the investigator or the patient). For patients who experienced mild or greater erythema the warts were more likely to clear completely; however, not all individuals whose warts cleared developed an erythematous reaction. Among the female patients treated with 5% imiquimod cream, the complete response rate was 17% (1 of 6) for those who never experienced erythema at the treatment site, while the complete response rates were 63% (5 of 8), 56% (5 of 9), and 89% (16 of 18) for those who experienced mild, moderate, or severe erythema at the treatment site, respectively ($P = 0.008$; Fisher's exact test). Similarly, among the male patients treated with 5% imiquimod cream, the warts of none (0 of 8) of those who experienced no erythema at the treatment site cleared completely, while the warts of 43% (3 of 7), 48% (10 of 21), and 60% (9 of 15) of those who experienced mild, moderate, or severe erythema, respectively, cleared completely ($P = 0.034$; Fisher's exact test). The most commonly reported wart-site reactions reported by patients were pain, itching, and burning at the application sites. In the 5% imiquimod cream group, pain was reported at least once by 34.8% of the patients, itching was reported by 32.6% of the patients, and burning was reported by 16.3% of the patients. The reported systemic reactions and laboratory abnormalities reported by patients in the 5% imiquimod cream group were not significantly different from those reported by patients in the vehicle group. Headache and upper respiratory tract infections were the most common systemic adverse reactions among patients in all groups. No patients discontinued therapy because of systemic adverse reactions. One patient (1%) in each of the imiquimod cream groups discontinued therapy because of local skin reactions.[15]

Conclusion

Based on study results, it can be concluded that Imiquimod 5% cream, as an immune response modifier, is safer than cryotherapy in the treatment of condylomata acuminata. A prospective multicenter evaluation with a larger sample size and a longer study period with long time follow-up are recommended.

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