Efficacy and safety of imiquimod versus podophyllum resin in the treatment of anogenital warts

A comparative study of efficacy and safety of imiquimod versus podophyllum resin in the treatment of anogenital warts

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INTRODUCTION
Anogenital wart is a common sexually transmitted infection caused by Human Papilloma Virus (HPV). HPV is a double-stranded DNA virus that causes cutaneous viral warts, most commonly located on the skin and genitalia.¹ Minor abrasions and infections promoted by maceration of the epithelia most frequently serve as conduits for HPV to the basal keratinocytes, the primary targets for HPV infection.² A variety of different strains and variants of HPV have been identified based on DNA studies and serological detection of type-specific antibodies against HPV capsid antigens. Over 118 types of papillomavirus have been identified.³ Different HPV types show a preference for either uncornified mucous membranes or cornified stratified squamous epithelium. More than 35 types of HPV infect the genital tract.⁴ Types 6 and 11 are associated with low risk anogenital warts, and types 16, 18, 31, 33, 45 and 59 are most commonly associated with squamous cell and adenocarcinomas of the cervix.⁵,⁶

There is huge armamentarium of treatment options available for warts. Cryotherapy, cautery, topical podophyllin are commonly employed methods for treatment of genital warts. Still definite evidence for effectiveness of available treatment options is lacking. None of the treatment has proven 100% cure rate. Pain and other side effects related to treatment of genital warts can be determining factors in choosing therapy.⁷

Topical imiquimod and topical podophyllotoxin are two most commonly used treatment options now a days. Topical imiquimod is relatively safer option which can be given to patient for home application safely as compare to podophyllotoxin which needs to be applied in office generally.

This study was undertaken with aims and objectives of comparing the effectiveness and safety of self-applied imiquimod 5% cream and clinician applied podophyllum resin 20% solution in external anogenital warts in either sex; using the parameters of

ABSTRACT

Background: Human Papilloma Virus (HPV) infection causing anogenial warts is a common sexually transmitted infection. Out of various treatment modalities used for anogenital warts, podophyllum toxin topical application has been most frequent and most successful. Recently available topical imiquimod has also shown to be equally effective with lesser side-effects as compared to podophyllum toxin. This study is done in patients with anogenital warts to compare the efficacy and side-effects of imiquimod v/s podophyllum toxin in adult patients with anogenital warts.

Methods: In patients presenting with anogenital warts, 20 patients each were treated with either topical imiquimod or topical podophyllum toxin. Results: Efficacy in both study group was comparable but side-effects were statistically low in imiquimod treated group. Conclusion: Both imiquimod and podophyllum toxin are equally effective for external anogenital warts but ease of application and fewer side-effects make imiquimod better suited for treatment of anogenital warts.

Key Words: Anogenital warts, imiquimod, podophyllotoxin

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This study was undertaken with aims and objectives of comparing the effectiveness and safety of self-applied imiquimod 5% cream and clinician applied podophyllum resin 20% solution in external anogenital warts in either sex; using the parameters of
clearance rates of warts and recurrence rates during post-treatment follow-up. Adverse effect profile of both formulations was also compared in this study.

MATERIALS AND METHODS
This study was done on 40 adult patients above age of 18 years and of either sex presenting in skin OPD for the treatment of external anogenital warts. 20 patients were randomly assigned to each treatment arm - Group A 5% imiquimod cream topical application thrice per week for maximum 16 weeks and Group B 20% podophyllum resin once a week for maximum 6 weeks. All patients were thoroughly examined clinically, detailed history of each patient with special emphasis on sexual behavior were noted, Serum HIV antibody and Serum RPR tests were done in all patients after counseling. Patients were randomized as odd number to Group A and even number to Group B.

Inclusion criteria used were patients of either sex above 18 years of age, having at least two external anogenital warts irrespective of HIV serology status and not used any prior treatment for present condition.

Exclusion criteria used were pregnant females and lactating mothers, history of convulsion or any neurological disease and prior treatment taken for present condition. Patients with co-existing genital ulcer or discharge were not included in the study.

In group A patients were advised to apply imiquimod 5% cream on warts thrice in a week (Monday, Wednesday and Friday) for 16 weeks or until clearance of warts whichever occurred early. After each application patients were advised to wash treated area with soap and water within 6 -10 hours. Patients were taught to apply medicine only on wart surface avoiding application on normal skin. All patients were called for follow up every week for first 4 weeks and then every 15 days for rest of the study period.

In group B patients were called to clinic once a week for application of podophyllum resin 20% by clinician, medicine was allowed to air dry after application before coming in contact with cloths. Patients were instructed to wash away with soap and water within 2 to 4 hours, treatment was continued for 6 weeks or until clearance of lesions whichever occurred early.

Pre-treatment assessment of lesions was done in the form of lesion count and area measurement. This assessment was repeated at each visit. All patients were regularly followed up once every month for 4 months after completion of treatment.

The primary end point was complete clearance of lesions at the end of treatment period.(16 weeks for imiquimod and 6 weeks for podophyllum resin). Secondary end point was wart free follow up period of 4 months.

RESULTS
Out of 40 patients included in the study 34 were male and 6 were female. Maximum numbers of patients were between 26-45 years of age. Minimum age was 19 years and maximum age was 50 years (Mean age 29.8 years) (Chart 1 A &B)

Fig.: 1 Chart 1 A & B showing age and sex distribution of patients

Chart 2 A and B shows patients’ literacy level and occupation respectively. Maximum patients had only primary education. Most of the female were housewives while most of the male were working as driver or laborer.
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Fig.: 2 A & B shows patients literacy level and occupation

Fig.: 3 A, B & C shows sexual practice and type of exposure in patients

Fig.: 4 showing duration of presence of lesions

Fig.: 5 A & B shows location of lesions in male and female

Fig.: 6 A shows clearance rate in group A and Chart 6 B shows clearance rate in group B
2 male patients were found to be HIV reactive. None of the patient had VDRL test positive. All 6 female patients had heterosexual exposure only; while most of male (91.2%) had heterosexual exposure, 3 (8.8%) had homosexual exposure (Chart 3 A). 17 (50%) male had commercial sex worker as probable source of infection while friends, spouse, neighbor were other sources in varying percentage (Chart 3 B).

Majority of patients (85%) had genitogenital type of intercourse (Chart 3 C). Majority of patients (n=34, 85%) presented within 6 months of development of lesions (Chart 4).

Most common location of warts in male was glans penis and/or prepuce (>60%); while in female 83.3% had lesions on vulva. Perianal warts were found in 4 male and 1 female. Other site involved in male was shaft of penis with or without prepucial involvement (Chart 5 A & B).

14 male and 2 female patients in group A (84.22%) while 11 male and 2 female patients in group B (65%) showed complete clearance. (Chart 6 A & B). (Figure 1a, 1b, 2a, 2b) Average time required for clearance of lesions was 6.75 weeks in Group A and 4.7 weeks in Group B. In post treatment follow up for 16 weeks, 4 patients in group A and 8 patients in group B had recurrence as shown in Table 7; which shows that recurrence rate was higher and earlier in podophyllum group as compared to imiquimod group. In group A mild erythema and itching were the only significant side-effects noted; while erytherma with erosions, edema, itching or burning and pain of mild to severe grade were seen in significant number of patients in podophyllum group. (Chart 8 A&B)

Statistically clearance rate was not significant between two groups as per analysis. (Chi-square=0.501, p value= 0.47) But the differences in side-effects between two treatment groups was statistically significant. Mild degree side effects - Chi square=0.40, p value=0.52. Moderate degree side effects-Chi square = 3.9, p value=0.04(significant). Severe degree side effects-Chi square=0.27, p value= 0.5

**Fig.:** 7 shows number of patients having recurrence at 4, 8 and 16 weeks in both groups

**Fig.:** 8 A shows side-effects in Group A, chart 8 B shows side-effects in Group B

**Fig.:** 1 a,b Female patient showing complete resolution of warts after podophyllum 6 weeks therapy
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Fig.: 2 a,b Male patient pre-treatment and complete resolution after 16 weeks imiquimod therapy.

Fig.: 3 severe edema, erythema and ulceration after application of podophyllum toxin

DISCUSSION

Treatment of genital viral warts is generally by means of destructive treatments like cryotherapy, salicylic acid application, phenol application, electrocautery or radiofrequency cauterization and most recently removal of lesions by fractional CO2 and other lasers. None of these available treatment options aim at inducing immune response against virus.

Podophyllum resin is particularly useful for treatment of genital warts where other therapeutic options are either not very effective or may have associated side-effects. The rhizomes of the mayapple plant (Podophyllum peltatum) that grows throughout eastern and midwestern North America are the source of podophyllin resin, the crude alcohol extract containing podophyllotoxin, 4-demethylpodophyllotoxin, α-peltatin and β-peltatin. Podophyllotoxin binds to microtubules and causes mitotic arrest in the metaphase of cell division.

Imiquimod is an imidazoquinoline. It is a cytokine inducer and modifier of innate immune response which enhance acquired antiviral and antitumor immune responses. It is a Toll-like receptor 7 agonist which works on viral warts by inducing production of local cytokines from predominantly Th-1 type of cells. Cytokines like TNF-alpha, INF-alpha, IL-1,6,8,10,12 stimulate tissue specific apoptosis of viral infected keratinocytes thus leading to reduction in viral load with subsequent regression and normalization of keratinocyte proliferation.

Regression of warts after treatment with imiquimod is strongly associated with evidence of tissue production of INF-α, -β, and -γ and TNF-α as well as a decrease in the presence of HPV DNA and in the expression of mRNA for both early and late viral proteins. Imiquimod in various studies has been shown to induce complete clearance of lesions in 37% to 52% patients with recurrence rate of 8.8% to 19% within 3 months. While podophyllin has been shown to induce regression in 41% to 72% patients with recurrence in 26% to 87% patients.

CONCLUSION

The present study confirms the previously available study results for imiquimod 5% cream and Podophyllum resin 20%; showing imiquimod to be equally effective as podophyllotoxin in efficacy but with lesser side-effects. Though podophyllin is considered 1st line treatment option for genital warts and many studies have shown both agents to be identical in efficacy and safety, Podophyllin has it’s own limitations like severe adverse effect profile and contraindication in pregnancy. So to our conclusion, imiquimod is better suited option for treatment of external anogenital warts as compare to podophyllotoxin. Advantages of using imiquimod 5% cream include less pain and trauma than other treatments, including podophyllotoxin, salicylic acid, cryotherapy or laser.
costs and pain of office-based procedures can be avoided as the imiquimod cream is self-applied.\textsuperscript{21}

REFERENCES