A prospective, open, comparative study of 5% potassium hydroxide solution versus cryotherapy in the treatment of genital warts in men*

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Abstract: BACKGROUND: Genital warts are caused by human papillomavirus infection and represent one of the most common sexually transmitted diseases. Many infections are transient but the virus may recur, persist, or become latent. To date, there is no effective antiviral treatment to eliminate HPV infection and most therapies are aimed at the destruction of visible lesions. Potassium hydroxide is a strong alkali that has been shown to be safe and effective for the treatment of genital warts and molluscum contagiosum. Cryotherapy is considered one of the most established treatments for genital warts. No comparative trials have been reported to date on the use of potassium hydroxide for genital warts.
OBJECTIVE: A prospective, open-label, randomized clinical trial was conducted to compare topical potassium hydroxide versus cryotherapy in the treatment of genital warts affecting immunocompetent, sexually active men.
METHODS: Over a period of 10 months, 48 patients were enrolled. They were randomly divided into two groups and selected on an alternative basis for either potassium hydroxide therapy or cryotherapy. While response to therapy did not differ substantially between both treatment modalities, side effects such as local pain and post-treatment hypopigmentation were considerably more prevalent in the groups treated using cryotherapy. Result: In our study, potassium hydroxide therapy proved to be at least as effective as cryotherapy and offered the benefit of a better safety profile.
CONCLUSION: Topical 5% potassium hydroxide presents an effective, safe, and low-cost treatment modality for genital warts in men and should be included in the spectrum of therapies for genital warts.
Keywords: Clinical protocols; Comparative study; Condylomata acuminata; Cryotherapy; Genital diseases, male; Intention to treat analysis; Male urogenital diseases

INTRODUCTION

Genital warts (GW) are the clinical result of human papillomavirus (HPV) infection, most commonly HPV types 6 and 11.[1-3] These viruses are sexually transmitted and infect the skin and mucous membranes of the external genitalia, as well as the peri and intra-anal area in both genders.[3-6] In addition, HPV types 16, 18, as well as several others, have oncogenic potential and are involved in the development of cervical, vulvar, penile and anal cancer.[5,7] As a human-specific DNA virus, HPV is incorporated into the genome of epithelial keratinocytes. Thus, destructive and immunomodulation topical therapies have been the standard of treatment. Complete clearing of GW is frequently not achieved.[8]

Treatment of warts poses a therapeutic challenge. No single therapy has been proven effective at achieving complete remission in every patient.[7,9] At present, there is no pharmacologic solution to eliminate definitely HPV from human cells. The ideal therapy should be effective (i.e., high clearance and low recurrence rates), non-traumatic, inexpensive and involve few local and systemic adverse effects.[10,11,12]

Potassium hydroxide (KOH) is a strong alkali that has been found to be effective, safe, and well tolerated in the treatment of different dermatoviruses, including molluscum contagiosum in children and genital warts in adults.[13,14,15] This is due to its ability to dissolve keratin and penetrate deeply the skin.[13,14,15] Furthermore, treatment is generally well tolerated and

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does not entail systemic side effects. Nonetheless, there are no comparative studies on the use of KOH for the treatment of GW.

Cryotherapy with liquid nitrogen is one of the most established treatments for GWs and clearance rates have ranged from between 54 and 88%.[16-20] It has been shown to be superior to electrodessication and podophyllin.[21,22] Systemic side effects do not occur.[13,14,19]

This comparative study seeks to evaluate the efficacy and safety of topical KOH versus cryotherapy for treatment of genital warts in sexually active men. Clearance rates, adverse reactions, and recurrence rates after a 30-day follow-up period were recorded.

METHODS AND MATERIALS

This prospective, open-label clinical trial was approved by the University of São Paulo General Hospital Institutional Review Board. The study was originally estimated based on the mean number of new HPV cases in men at the department within a 10-month period. All patients read and signed an informed consent form. Male patients aged over 18 with one or more genital warts were included in the trial. Patients with urethral or peri-anal lesions, as well as a positive status for HIV, syphilis, hepatitis B, or hepatitis C, and diabetes or any other immunosuppression, were excluded from the study. Over a period of 10 months, from February to December of 2009, 48 patients were enrolled. They were randomly divided into two groups. Patients were selected on an alternative basis for either KOH or cryotherapy.

Cryotherapy with liquid nitrogen was applied by the same physician in all patients. Treatment cycles ranging from 5 to 20 seconds were carried out, depending on the size of each single lesion, until a 1 mm halo was achieved. Each cycle was repeated every two weeks until all lesions cleared, with a maximum treatment period of three months. In the KOH group, patients were shown how to apply KOH 5% aqueous solution using a toothpick with cotton wrap on the tip, and instructed to use the medication daily until mild inflammation was observed. The process was repeated for three months or until complete regression was observed. Each patient received a 10 ml flask containing a 5% KOH aqueous solution.[14]

In both groups, follow-up visits occurred every two weeks until all lesions cleared, or for a maximum of 3 months. Patients were seen one month after treatment completion to check for recurrences. At each visit, the number of lesions and local and systemic effects, were recorded. If new lesions developed during the study, these were also treated and included in the data.

The results were included in tables and analyzed by Chi-square and Fisher's tests. In the results evaluation, a confidence interval (CI) of 95% was considered statistically significant.

RESULTS

A total of 48 patients with GW, aged 18 to 74 (average age: 31.1 years), were included in this study. The number of lesions ranged between 1 and 20 (average of 6.5 lesions). Localization included the glans, foreskin, penile shaft, and pubic and scrotal area.

The KOH group included 24 patients aged 21 to 74 years (mean 32.7 years and standard deviation of 11.0). The number of lesions ranged from 1 to 20 (mean 5.7 lesions and standard deviation of 5.3) and the size of the lesions ranged from 1 to 30mm (mean 10.6mm and standard deviation of 7.2). Signs and symptoms of inflammation such as erythema, edema, pain, or stinging sensations occurred one to three days after initiating therapy. Twenty patients (83.3%) completed the study. The duration of treatment until patients were completely wart-free ranged from 2 to 12 weeks (mean 6.9 weeks). Four patients (16.7%) did not return after the first visit and were considered treatment failures. Seven patients (29.2%) had persistent lesions after 3 months of treatment and were also considered treatment failures. Of the patients with complete clearance of GW, no recurrences were observed at the one-month post-treatment follow-up visit. At the end of the trial, 54.2% of treated patients in the KOH group were completely wart-free without recurrences (Figures 1 to 4). Superficial erosions were present in 50%, mild pain or stinging was reported in 16.7% and post-treatment hypopigmentation occurred in 16.7% of treated patients.

The cryotherapy group included a total of 24 patients aged 18 to 48 years (mean 28.7 years and standard deviation of 9.6). The number of lesions ranged from 1 to 20 (mean 7.4 lesions and standard deviation of 6.0) and the size of the lesions ranged from 1 to 25mm (mean 9.6mm and standard deviation of 6.2). Twenty-two patients (91.7%) completed the study. All patients experienced mild to moderate pain during cryotherapy application. Signs of inflammation (erythema and edema) occurred between 24 to 48 hours later. Duration of treatment ranged from 2 to 12 weeks (mean 9.6 weeks). Two patients (8.3%) did not return after the first visit. Eight patients (33.3%) had persistent lesions after 3 months of treatment, and two patients (8.3%) presented with new lesions at the one-month post-treatment follow-up visit. All twelve of these patients (50%) were considered treatment failures. At the end of the trial, 50.0% of cryotherapy-treated patients were completely wart-free without recurrences (Figures 5 and 6). Superficial erosions were reported in 37.5% of all patients treated, mild to moderate pain in 100% and hypopigmentation in 45.8%.

DISCUSSION

Current data suggest that visible genital warts are present in approximately 1% of sexually active

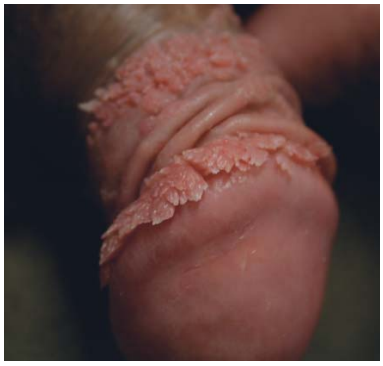

Figure 1: Before KOH 5% treatment

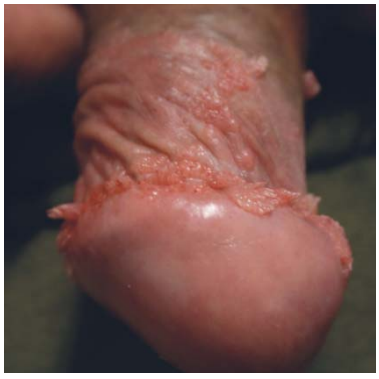

Figure 2: Before KOH 5% treatment

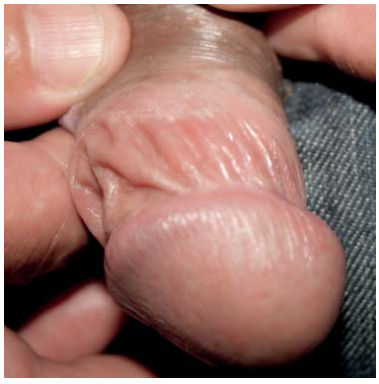

Figure 3: After KOH 5% treatment

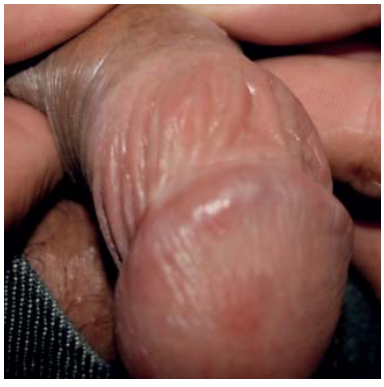

Figure 4: After KOH 5% treatment

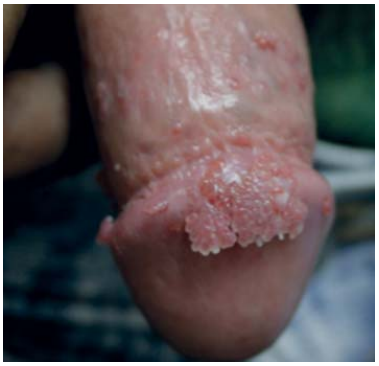

Figure 5: Before cryotherapy treatment

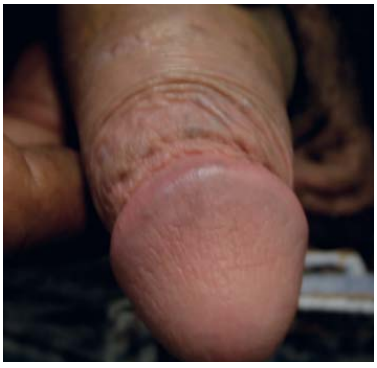

Figure 6: After cryotherapy treatment

adults in the United States and an additional 15% has subclinical infection.[1,3] Minor breaks in the skin are thought to be important in the establishment of HPV infection.[2] The incubation period has been reported to vary between 2 weeks to 8 months.[4]

There are no established treatments capable of eliminating HPV from human cells. HPV vaccines based on virus-like particles can only act in a prophylactic manner. Thus, destructive therapies and immunomodulatory agents have been the standard of treatment for several decades.

Therapies for GW are generally recommended based on considerations of efficacy, adverse events, cost and recurrence rates.[10-12] Patient-applied topical treatment modalities have included podophyllotoxin, salicylic acid, imiquimod, polyphenon E, 5-fluoracil, and KOH, among others.[23-27] Physician-administered destructive methods have mostly included cryotherapy, electrosurgery, intralesional bleomycin, lasers, and diphencyprone.[28-30]

The aim of this study was to compare the efficacy and safety profile of a recently described patient-applied treatment modality, namely topical KOH solution with physician-administered cryotherapy - one of the most established and efficient therapies for genital warts.[13,16,18,19,31] In randomized controlled trials using cryotherapy for GWs, clearance rates of 54– 88% and recurrence rates of 21–40%, have been reported

with monotherapy.[18,20]

In this study, patients were randomized into two groups with similar characteristics, including age, mean number and lesion size. Despite the participation of a 74-year-old patient in the KOH group, this does not increase significantly the mean values and standard deviations of the group. Hence, the two groups were statistically similar and comparable in terms of age, number and size of lesions. No statistical difference in efficacy between the KOH and the cryotherapy treated groups was observed (Table 1). There was a success rate of 65% in the first group (KOH) compared with 54.7% in the second group (cryotherapy). The KOH group showed a lower average for treatment duration (mean 6.9 vs. 9.6 weeks). No recurrences were seen in the KOH group, while the cryotherapy group presented a 10% recurrence rate.

The most significant differences between the groups concerned safety. Cryotherapy patients complained of more pain (100% vs 16.7%; Table 1) and residual hypopigmentation (45.8% vs 16.7%; Table 1) than KOH-treated patients. KOH patients presented superficial erosions more often than the cryotherapy group (50% vs 37.5%; Table 1). It is considered that erosion results from the digestive properties of KOH. This side effect was entirely expected, just as pain and hypopimentation were expected in the cryotherapy group.

Table 1: Comparison of treatment with 5% KOH and cryotherapy for genital warts in men

	Successfully Treated	Pain	Hypopigmentation Present	Erosions	Total number of patients
KOH 5%	13	4	4	12	20
Cryotherapy	12	22	11	9	22
TOTAL	**25**	**26**	**15**	**21**	**42**

CONCLUSIONS

Our findings regarding treatment of GW in sexually active men provide insight into a new method of treatment, namely KOH therapy. In this study, KOH therapy proved to be at least as effective as cryotherapy in treating GWs, with the further benefit of being safer. However, since the sample was limited, more studies need to be conducted. Topical 5% KOH is an effective, safe, and low-cost treatment modality and should be considered in the therapeutic arsenal against GWs in men.

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