Cryotherapy versus Podophyllin in the Treatment of Genital Wart

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تاریخ ارائه : ۸۵/۲/۲۱ تاریخ پذیرش : ۸۶/۵/۱

مقایسه سرمادرمانی با پودوفیلین در درمان زگیل تناسلی

خلاصه

مقدمه: زگیل تناسلی یکی از بیماریهای شایع منتقله از راه جنسی است که توسط ویروس پاپیلومای انسانی ایجاد می شود. پودوفیلین عصاره گیاهی است که از دیر باز در درمان زگیل تناسلی مورد استفاده قرار می گرفته است. این دارو خاصیت جلوگیری کننده از تقسیمات سلولی (آنتی میتوتیک) داشته و اثر مستقیمی بر سلولهای اپی تلیال دارد. از طرفی نیتروژن مایع که ماده ای است که بطور وسیع در سرما درمانی (کرایوتراپی) استفاده می شود، موجب مرگ سلولی، ایجاد کریستالهای مایع در داخل سلول و آسیب اجزای آن می گردد. این مطالعه با هدف ارزیابی اثر بخشی محصول پودوفیلین با سرما درمانی با نیتروژن مایع در درمان زگیل های تناسلی انجام شده است.

روش کار: این مطالعه کارآزمایی بالینی، از بهمن ۱۳۸۲ – دی ماه ۱۳۸٤ در درمانگاه پوست بیمارستان قائم (عج)، بر ۷۰ بیمار مبتلا به زگیل تناسلی انجام شد. ۳۵ بیمار به طور تصادفی محلول پودوفیلین دریافت کرده و ۳۵ نفر تحت درمان با کرایوتراپی با نیتروژن مایع قرار گرفتند. مصرف دارو هفته ای یک بار تا پاک شدن کامل ضایعات و یا حداکثر دوره ۸ هفته ای ادامه داشت. سپس بیماران تا ده هفته از نظر احتمال عود مجدد پیگیری می شدند.

نتایج: زمان متوسط بهبود کامل ضایعات ۳/۹ هفته (۱– ۷ هفته) برای پودوفیلین و ٤/۹ هفته (۱–۹ هفته) در گروه سرما درمانی بود (p=۰/۰۳۹). از میان بیماران دو گروه که به طور کامل درمان شده بودند و یا آنها که دوره ۱۰ هفته ای پیگیری شان به سر رسیده بود ۲٦٪ و ٤۷٪ به ترتیب در دو گروه پودوفیلین و سرما درمانی عود را تجربه نمودند (p<۰/۰۵). واکنشهای التهابی موضعی به طور قابل توجهی در گروه سرما درمانی بیشتر از پودوفیلین بود.

نتیجه گیری: طبق نتایج به دست آمده محصول پودوفیلین در درمان زگیل تناسلی موثر بوده و عوارض و احتمال عود کمتری نسبت به کرایوتراپی با نیتروژن مایع دارد.

کلمات کلیدی: سرما درمانی، پودوفیلین، زگیل تناسلی

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Introduction

Genital human papilloma virus (HPV) infection is probably one of the most common infections that can be sexually transmitted. More over, because of its clear association with cervical cancer in women and its potential association with other anogenital malignancies it is an important public health problem (1, 2).

It has been estimated that 30% to 50% of sexually active adults have genital human papiloma virus (HPV) infection and 1% have genital wart (3).

Patients are often asymptomatic but may have discomfort, discharge or bleeding. The typical anogenital wart is soft, pink, elongated, and sometimes filliform or pedunculated. The lesions are usually multiple especially on moist surfaces and their growth can enhance during pregnancy (4) or in the presence of other local infections (5, 6).

Genital wart may clear without therapy. This is thought to be mediated by immunologic responses (7).

A variety of treatment methods are available for genital wart. Podophyllin is a plant derived resin containing several cytotoxic compounds. It is more effective on mucosal than keratinized surfaces. It acts as an anti-mitotic, disrupting the formation of the spindle on which chromosomes align at mitosis. Podophyllin resin is used as solution of 10-25% in compound tincture of benzoin for treatment of genital wart. Podophyllin is generally ineffective if applied to wart of other types (8).

Liquid nitrogen is most widely used as the cryotherapy agent because of its easy usage, inexpensiveness and readily availability to very low temperature (-196); it also works faster than other methods.

The extent of injury is determined by the rate of freezing, the coldest temperature reached, the freeze time, and the rate of thawing. Maximum damage reduction is made by rapid freezing and slow thawing; repeating the freeze cycle reduces greater tissue damage (9).

The purpose of this study was to evaluate the efficacy of podophyllin solution versus liquid nitrogen cryotherapy on genital warts.

Material and Methods

This prospective clinical trial was performed from February 2003 to December 2005 in Dermatology Clinic of Qaem Hospital, Mashhad university of Medical Sciences. A total of 70 female patients with external genital wart entered the trial. The diagnosis of genital warts was established by physical examination and confirmed by histopathology when indicated. Only clinically visible, external anogenital warts were evaluated and treated. The wart area was determined by measuring the two greatest perpendicular dimensions of each wart and taking the product of these two measurements. Total wart area was the sum of areas for each wart. The patients divided randomly into two groups. Those who had documented hypersensitivity, diabetes, impaired peripheral circulation, total lesion area > 400 mm^2, any individual lesion with an area of >100mm^2, intrameatal or vaginal warts, or if being pregnant were excluded. A solution of 25% podophyllin in compound tincture of benzoin was applied accurately and in enough amounts to cover the wart area, then allowed to dry for a few minutes and washed out after 4 hours. In cryotherapy, cotton wool was dipped in the liquid nitrogen and applied to wart area for two short freeze – thaw cycles, being held until a white halo area appeared around the circumference of the lesion (about 10 to 20 seconds). In both groups treatment was repeated weekly and continued until complete clearing of lesions or for a maximum treatment period of 8 weeks. In each visit, the wart evaluation and skin irritation assessed, so patients were queried regarding adverse events and concomitant medications as well as pain, itching and burning at the site of agent application or adjacent area. During each visit they were asked to quantify these symptoms as mild, moderate or severe. Patients who experienced

complete clearance of warts, during the treatment period, entered a free follow up treatment for a period of 10 weeks (or less if no recurrence was noted).

Data entry and coding was done and it was analyzed by SPSS version 9. Student t-test, χ^2 test and mann-withney were used for the statistical analysis. Statistical significance was defined as $p<0.05$.

Results

From the total of 70 patients who entered the trial, only 59 female patients completed the trial (11 patients who, discontinued for personal reasons, judged to be noncompliant with dosing schedules or failed to follow-up were excluded from the analysis). There was no significant difference between two groups with regard to the age. The mean age of podophyllin group was 25/6 years (range of 17-47 years) and cryotherapy grouping 25/5 years (range of 16-37 years). Of patients 22 were single and partner of 32 were affected.

In podophyllin group 3 patients and in cryotherapy group 6 patients had history of previous genital wart, also 6 patients in podophyllin group and 5 patients in cryotherapy group had history of previous nongenital wart and 2 patients in each group had history of previous herpes genital infection. Number of warts and baseline wart area in podophyllin and cryotherapy group were 9.7 (range 9-20), 101 mm² (range15-385) and 9.5 (range 3-16), 328 mm² (11-234), respectively.

The commonest presentation of wart were papule in 21 and 19 patients of podophyllin and cryotherapy groups respectively. However only one patient in each group had condyloma acuminatae. The most common sites of lesions were perineum (23 patients), vestibule (22 patients) and least common sites were inguinal (55 and 56 patients in podophyllin and cryotherapy group respectively) (Table 1).

Table 1: Site of wart lesions in two groups of patients, in Dermatology Clinic of Qaem Hospital, Mashhad, Feb 2003 to Dec 2005

Site of wart	Podo phyllin	Crytherapy	Chi-squre test
Mons publis	18	19	0.62
Labia major	8	12	0.45
Prineum –vestibule	23	22	0.17
Labia minor	13	16	0.72
Vagina orifice	12	13	0.25
Perianal	12	11	0.97
Inguinal	5	6	0.60
Thigh	11	5	0.12

The mean duration of wart before therapy for podophyllin and cryotherapy groups was 4.7 weeks (range of 1-12) and 4.3 weeks (range of 1-12), respectively.

The mean duration of complete clearance was 3.9 weeks (range of 1-7) for podophyllin and 4.9 weeks (range of 1-9) for cryotherapy groups ($p=0.039$) (Fig1).

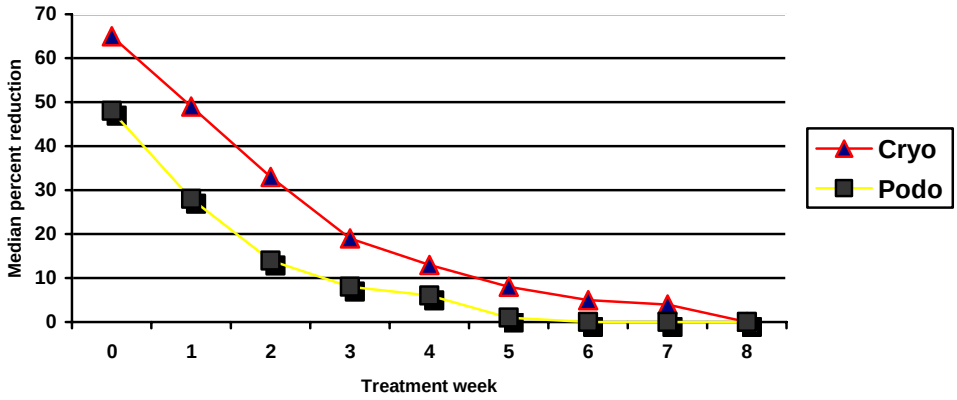

Figure 1: Median percentage reduction in baseline wart area in both groups. In Dermatology Clinic of Qaem Hospital, Feb 2003 to Dec 2005

Adverse reactions of two regimens are showed in Table 2.

Table 2: Application – site reactions and intensity, in Dermatology Clinic of Qaem Hospital, Mashhad, Feb 2003 to Dec 2005

Sign or symptoms	**Incidence for podophyllin therapy group**	**Intensity of reaction**			**Incidence for cryo therapy group**	**Intensity of reaction**			**p.value**
		Mild	moderate	Severe		mild	mode rate	severe	
Pain	6	5	1	0	18	16	2	0	*0.001
Itching	26	23	3	0	15	14	1	0	*0.012
Burning	29	23	6	0	28	18	8	2	*0.074
Erosin	5	0	0	0	9	0	0	0	**0.14
Erythema	8	0	0	0	12	0	0	0	**0.16

*Mann whitney test ** Chi –square

At the end of treatment overall side effects were more frequent in cryotherapy. At this course Patients were followed up for 10 weeks. In patients treated with cryotherapy, Vecurrence was more frequent (12 patients versus 8 patients in podophyllin group).

Discussion

Most genital HPV infections occur during the first few years after the onset of sexual activity (10, 11).

In this study the mean age of patients was 25 years. From the total of 70 patients, 32 of them had affected partner. Considering the high sexual infectivity of anogenital wart, abstinence from intercourse or usage of condom until visible lesions are cleared, and evaluation about infection of partner are necessary (12).

The primary goal of treatment is to ameliorate symptoms and remove symptomatic warts, although it is unknown whether it affects subsequent transmission or the natural course of HPV infection (13).

A wide variety of therapies are available to treat genital warts. In current study, the efficacy of readily available agents: Podophyllin and cryotherapy was assessed.

The results showed that, podophyllin therapy was more effective than cryotherapy. The

Mean duration of treatment was 1 week lesser in podophyllin than cryotherapy group (p=0.039), while recurrence was more frequent in cryotherapy group (12 versus 8 patients in podophyllin therapy group).

Podophyllin resin has been evaluated to be extensively relevant to other treatment methods (14, 15), when compared individually with podofilox, cryotherapy and electro surgery, or when used with intralesional IFN as an adjunct therapy. These treatment methods were statistically equivalent to podophyllin alone (16). Recurrence had been reported for 23-65% of clinical trial participants. Cryotherapy was found to be more acceptable than electrocautery, although the success rate with these two methods is comparable. The clearance rate of cryotherapy ranges from 63% to 91 % (16).

Hadley, et al (17) and Eron, et al (18), each reported data for comparison groups who received cryotherapy versus placebo; In their studies wart clearance respectively was 40% after 3 months and 27% after 6 months. Data have suggested that recurrence rates maybe 38-73% by 6 month treatment (17, 18). These data are comparable with the present study's results, 26% and 41% recurrence with podophyllin and cryotherapy respectively.

In the study of Bashi SA., cryotherapy had shorter period of treatment versus podophyllin (19). While in this study the course of treatment was shorter and side effects were less prominent and recurrence was less frequent in patients treated with podophyllin.

Conclusion

Thus according to the results of this study, podophyllin is a more appropriate treatment for genital warts versus cryotherapy.

Abstract

Introduction: Genital wart is a common sexually transmitted disease caused by human papiloma virus. Podophyllin is a plant extract, having been traditionally used to treat genital wart. Podophyllin is an anti- mitotic agent with direct effect on epithelial cells. Liquid nitrogen is most widely used as cryotherapy agent. Cryotherapy causes cell death, ice crystals formation in the cell, and cellular components damages. The purpose of this study was to evaluate the efficacy of podophyllin solution versus liquid nitrogen cryotherapy on genital warts.

Material and Methods: This clinical trial was performed from Feb 2003 to Dec 2005, on 70 patients with genital wart in Dermatology Clinic, Qaem Hospital. Patients divided into two groups randomly. Of the total patients, 35 received podophyllin solution and another 35 treated with liquid nitrogen cryotherapy. Study medication was applied once weekly until the complete clearance of lesion for a maximum duration of 8 weeks. Patients whose warts cleared completely were observed for up to 10 weeks to determine the recurrence rate.

Result: The mean duration of complete clearance was 3.9 weeks (range 1-7) for podophyllin and 4.9 weeks (range 1-9) for cryotherapy group (P=0.039). Of podophyllin and cryotherapy treated patients, whose wart cleared completely and who finished 10 week follow up period, 26% and 47 % experienced the recurrence of warts, respectively (P>0.05). Cryotherapy patients experienced a significantly greater number of local inflammatory reactions than the podophyllin group.

Conclusion: This data indicated that podophyllin solution therapy of genital wart is more effective, with less recurrence rate and side effects, than liquid nitrogen cryotherapy.

Key words: Cryotherapy, Podophyllin, Genital Wart

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