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Original Article

Dermatology Section

A Comparative Study of Liquid Nitrogen Cryotherapy as Monotherapy versus in Combination with Podophyllin in the Treatment of Condyloma Acuminata

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ABSTRACT

Introduction: Condyloma Acuminata (CA) is a common viral sexually transmitted disease. Although various treatment modalities are available for treating CA, but none of them can achieve 100% response rate. In a search for better response rate and less recurrence rate, the combination of cytotoxic agent Podophyllin with ablative liquid nitrogen cryotherapy was evaluated over cryotherapy alone.

Aim: To evaluate the synergistic effect of Podophyllin as a chemotherapeutic adjunct to an ablative therapy of liquid nitrogen cryotherapy versus liquid nitrogen cryotherapy alone in the treatment of CA.

Materials and Methods: Sixty patients with multiple CA were randomly assigned to two groups in the study. Thirty patients in group A received double freeze thaw cycle of 25 seconds of liquid nitrogen cryotherapy. Thirty patients in Group B were subjected to liquid nitrogen cryotherapy in a similar manner followed by application of not more than 0.5 ml of 25% Podophyllin solution. All patients were followed up at 1, 4, 8, 12 and 24 weeks after the treatment to monitor the response to therapy and evaluation for any recurrence. When the number of unresponsive lesions were more than 30% of original lesions at 4 weeks follow-up, then the whole procedure was repeated again.

Results: The complete response rate and the recurrence rate in the Group B in our study were comparable to Group A as the difference was statistically insignificant. But the differentiating point was that the similar results were obtained in Group B with an average1.2 sessions per patient in comparison to an average of 1.67 sessions per patient in Group A.

Conclusion: Cryotherapy represents a simple, safe and effective regimen for the treatment of multiple CA which in combination with Podophyllin is even more effective as a single session procedure; thereby shortening the treatment regimen.

Keywords: Cryoablation, Genital warts, Human papilloma virus

INTRODUCTION

Condyloma Acuminata (CA) (syn.-anogenital warts, external genital warts), the most common sexually transmitted viral disease of genitalia is caused by Human Papilloma Virus (HPV) [1]. In recent times, CA 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. The worldwide prevalence of infection with Human Papilloma Virus (HPV) in women without cervical abnormalities is 11-12% [2]. Genital warts are sexually transmitted; with transmission rates of 60%, but materno-fetal transmission may also occur [3]. The incubation period varies from 2 weeks to 8 months [1].

Genital epithelial infections are caused by different HPV serotypes [4]. Most of these External Genital Warts (EGW) are caused by serotypes with low oncogenic potential but rarely HPV serotypes with high oncogenic potential (Type16 and18) are associated [5]. The spectrum of disease varies from subclinical infection to active disease [6]. 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 [6]. There is 12.2% risk of vertical transmission of HPV to a neonate delivered by normal vaginal route [7]. Thus, elective caesarean section may be a preferred mode of delivery in such cases [8].

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 [9]. The goal of treatment is clearance of visible warts; as it may decrease the infectivity if not oncogenicity [10]. A wide range of therapeutic options are available for treatment of CA 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]. Although a large armamentarium of therapies is available for EGWs, but no definitive therapy has emerged as the ideal standard of care in the treatment of CA. All methods are fraught with the uncertainty of achieving a complete cure and high possibility of recurrence of lesions [11].

Cryotherapy uses subzero temperature to 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 [12]. Among various cryogens available, liquid nitrogen and nitrous oxide are being commonly used for treatment of CA [13]. Liquid nitrogen can be applied with a cotton swab or as a fine spray over the lesion extending about 1–2 mm in the perilesional area for 30–60 seconds [14]. It is the most recommended line of therapy for CA 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 hypopigmentation and hyperpigmentation, particularly in black skin [12].

Podophyllin (PD) is a purified plant resin derived from *Podophyllum peltatum* and *Podophyllum emodi* [15]. It acts by linking to the microtubule protein of the infected cell which leads to the arrest of

mitosis in the metaphase culminating into epithelial cell death [13]. It is applied as paint directly to affected areas and left for some time. Because of possibility of local irritation and systemic toxicity, the compound must be washed off within 4-6 hours [15].

The major reason for treatment failure of CA 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 [16]. High rates of recurrence are noted in promiscuous, pregnant and immunocompromised patients [3].

Since all available treatment modalities have shortcomings, various combination therapies are being employed in treating CA [3]. The present study was undertaken to evaluate the synergistic effect of Podophyllin as a chemotherapeutic adjunct to an ablative therapy of liquid nitrogen cryotherapy versus liquid nitrogen cryotherapy alone in the treatment of CA.

MATERIALS AND METHODS

It was a prospective comparative study conducted in the Dermatology Department after prior ethical approval from institutional committee. Sixty clinically diagnosed patients of CA were enrolled in the study at random irrespective of age, sex and duration of disease for the study.

The patients presenting with warts in and around external genitalia, anus, urethral meatus and vagina in the STD clinic were scrutinized for the present study. Pregnant or lactating females, patients suffering from severe anemia, Diabetes Mellitus, Immunosuppression, HIV, HCV or Hepatitis B infection or having history of any prior treatment of CA in previous six months were excluded from the study. In case of any concomitant sexually transmitted disease like Candidiasis, Trichomoniasis etc., it was first treated and then the patient was included in the study.

After taking an elaborate history, conducting clinical examination and relevant investigations like complete blood counts, viral markers and biochemical investigations, a pre-informed and written consent was taken. The cases were then randomly assigned to two groups of 30 patients each i.e., Group A and Group B.

In patients of group A, the lesions were cleaned with 5% Povidone Iodine solution followed by injection of local anesthesia with 2% lignocaine solution in each lesion. Liquid nitrogen was sprayed using Cryogun, in a paint brush manner over all the lesions or the confluence of lesions. The lesions were sprayed from a distance of 1cm to freeze the wart tissue along with a 5mm halo of surrounding healthy tissue for a freeze time of 25 seconds [Table/Fig-1]. The lesions were allowed to thaw completely and were subjected to another 25 seconds freeze thaw cycle. Immediately after the procedure, the treated lesion was covered with cold saline packs for ten minutes. The patient was observed for another ten minutes for immediate pain, oedema, erythaema and bulla formation.

In the patients of Group B, each wart was sprayed with double freeze thaw cycles of liquid nitrogen twice in the same manner as mentioned in group A. After complete thawing of 2nd cycle, glycerin was applied to the surrounding areas of the lesions. A 25% PD in tincture Benzoin solution was taken in a container and its generous coat was applied to the lesions with a cotton bud taking precaution that total amount of PD should not exceed 0.5ml at any one session. It was allowed to air-dry and was subsequently covered with a single layer of gauze piece. The lesions were washed with soap and saline 2 hours after the procedure so as to remove as much PD as possible.

Post-procedure care: Patients in both groups received broad spectrum oral antibiotics and non-steroidal anti-inflammatory drugs for 7 days along with local washes of 5% Povidone Iodine followed by antibiotic skin ointment twice daily till the wound healed. In addition, the Group B patients were assessed for any neurological symptoms and haematological and biochemical investigations were repeated at 48 hours so as to monitor PD toxicity.

Follow up: Follow-up evaluations were conducted at 1, 4, 8, 12 and 24 weeks after the treatment to monitor the response to therapy and any recurrence. At each visit, the patients were assessed for severity of pain, oedema, erythaema, bullae formation, secondary infection and crust formation, in completeness regarding treatment of lesions, pigmentary changes, scarring and appearance of new lesions, if any.

At 4 weeks follow-up, in case the unresponsive lesions were more than 30% of the total number of original lesions, the whole procedure was repeated again in both groups. During the study period of 24 weeks, patients were advised to practice condom protected sexual intercourse only.

At the end of the study, the results achieved were recorded and were statistically analysed using the SPSS17.0 software. While evaluating results by applying Chi-square test, the statistical significance was set at $P<0.05$ and at Confidence Interval (CI) of 95%.

RESULTS

Sixty patients suffering from Condyloma Acuminata were enrolled in the study and randomly assigned to two groups of 30 patients each. Group A underwent Liquid Nitrogen cryotherapy as monotherapy while Group B patients were subjected to Liquid Nitrogen in combination with Podophyllin and were followed up as per the protocol mentioned in material and methods.

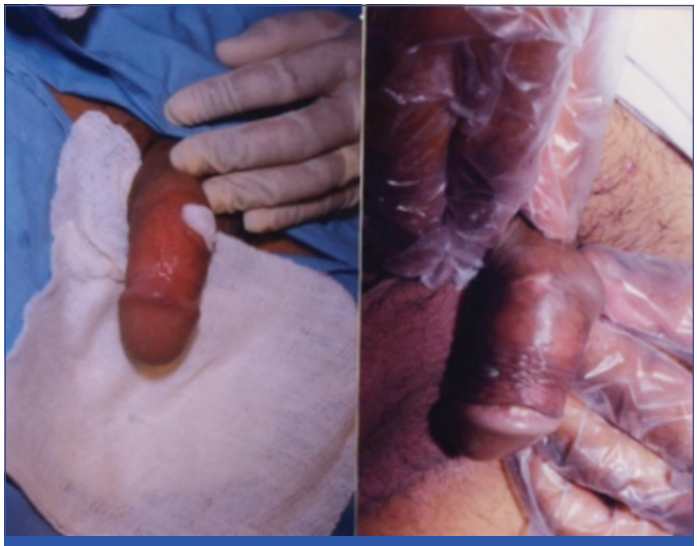
Demographic and Baseline Characteristics

Both the treatment groups were comparable for the demographic and baseline disease characteristics as shown in [Table/Fig-2]. Using chi-square tests, the structure equality of two treatment groups was tested with regard to the baseline characteristics.

Efficacy Assessment

The indicators of efficacy were the complete response rate of wart lesions and the recurrence rate of these warts as shown in [Table/Fig-3]. Lesions were designated as 'complete response' if all of the warts disappeared. A recurrence was defined as the occurrence of new lesions at previously treated or new sites. The complete response rate is a percentage of the number of the warts that had been cleared completely over the total number of the warts. The recurrence rate are a percentage of the number of recurrent warts over the total number of the warts [17].

In our study, the complete response rate in the combined cryotherapy plus Podophyllin group (85.18±9.59%) was lower



[Table/Fig-1]: Freezed wart tissue along with a 5mm halo and the subsequent scarring.

Characteristics		Group A	Group B	p-value
Age (years)		23.93±3.49	28.67±9.82	0.089NS
Sex	Female	14 (46.7%)	12 (40.0%)	0.713NS
	Male	16 (53.3%)	18 (60.0%)	
Duration of illness (Months)		4.7±2.59	5.5±3.27	0.464NS
Mean age of initiation of sex		20.20±2.08	21.73±3.03	0.118NS
History of Sexual promiscuity		18 (60%)	16 (53.3%)	0.713NS
Total number of lesions		408	474	
Number of External genital lesions		352	422	
Number of Anal lesions		40	32	
Number of Urethral meatal lesions		10	4	
Number of Vaginal lesions		6	16	

[Table/Fig-2]: Demographic and baseline disease characteristics of the patients.

Characteristics		Group A (n=30)	Group B(n=30)	p-value
Total no. of lesions		408	474	
Number of external genital lesions		352	422	
Complete response of external genital lesions	4 wks	256 (71.74±19.86%)	312(77.11±14.47%)	0.421
	8 wks	296 (85.20±9.17%)	350 (83.40±9.50%)	0.615
	12 wks	304(88.18±9.16%)	364(86.08±8.39%)	0.534
	24 wks	312(91.30±8.77%)	364 (86.41±8.92%)	0.156
Recurrence rates in external genital lesions		30 (6.74±6.88%)	38(10.20±8.53%)	0.248
Untreated lesions at 24 weeks		10	20	
Number of anal lesions		40	32	
Complete response of anal lesions	4 wks	24(59.72±8.33%)	24(78.27±14.88%)	0.073
	8 wks	30(75.00±21.52%)	26(86.61±15.53%)	0.415
	12 wks	32(77.78±20.79%)	26(86.61±15.53%)	0.522
	24 wks	36(93.05±8.33%)	24(74.11±20.49%)	0.138
Recurrence rates in anal lesions		4(6.94±8.33%)	4(18.75±23.94%)	0.387
Untreated lesions at 24 weeks		0	4(18.75%)	
Number of urethral meatal lesions		10	4	
Complete response of urethral meatal lesions	4 wks	10(100%)	4(100%)	-
	8 wks	6(66.67±28.87%)	4(100±0.00%)	0.219
	12 wks	6(66.67±28.87%)	2(50±70.71%)	0.724
	24 wks	8(83.33±28.87%)	0(0%)	0.030*
Recurrence rates in urethral meatal lesions		2(16.67±28.87%)	4(100±0.00%)	0.030*
Untreated lesions at 24 weeks		0	0	
Number of vaginal lesions		6	16	
Complete response of vaginal lesions	4 wks	2(25.00±35.35%)	8(53.33±18.86%)	0.423
	8 wks	0(0%)	14(90.00±14.14%)	0.012*
	12 wks	0(0%)	14(90.00±14.14%)	0.012*
	24 wks	0(0%)	14(90.00±14.14%)	0.012*
Recurrence rates in vaginal lesions		6 (100%)	2(10.00±14.14%)	0.423
Untreated lesions at 24 weeks		0	0	
Total complete response rate		356 (89.20±10.08%)	402(85.18±9.59%)	0.273
Total recurrence rates		42 (7.01±6.40)	48(11.55±9.50%)	0.137
Number of patients requiring 2nd session of treatment		20 (66.67%)	6(20.00%)	0.010*

[Table/Fig-3]: Efficacy assessment in two treatment groups.
(*:p < 0.05; Significant)

than cryotherapy monotherapy group (89.20±10.08%); but the difference was insignificant (p–value=0.273). Similarly, the recurrence rate for the combined cryotherapy plus Podophyllin group (11.55±9.50%) was higher than the recurrence rate of cryotherapy monotherapy group (7.01±6.40%); but this difference was again statistically insignificant (p–value=0.137). But the response rate was achieved at a faster rate in combination therapy group than in monotherapy group. At 4 and 8 weeks, higher improvements in the mean percentages of CA lesions were noticeable in cryo-Podophyllin combination group as compared to cryotherapy monotherapy, but at 24 weeks the results were almost comparable in both study groups.

Regarding the complete response and recurrence rates in the four classified locations in our study, the complete response and recurrence rates in cryotherapy monotherapy group were 91.30±8.77% and 6.74±6.88% in the external genitals and 86.41±8.92% and 10.20±8.53% in combination group; the complete response and recurrence rates in the anal area were 93.05±8.33% and 6.94±8.33% in cryotherapy monotherapy group and, 74.11±20.49% and 18.75±23.94% in combination group; the complete response and recurrence rates in the urethral meatal area were 83.33±28.87% and 16.67±28.87% in cryotherapy monotherapy group and, 0% and 100% in combination group; the complete response and recurrence rates in the vaginal lesions were 0% and 100% in cryotherapy monotherapy group and, 90.00±14.14% and 10.00±14.14% in combination group.

Tolerability Assessment

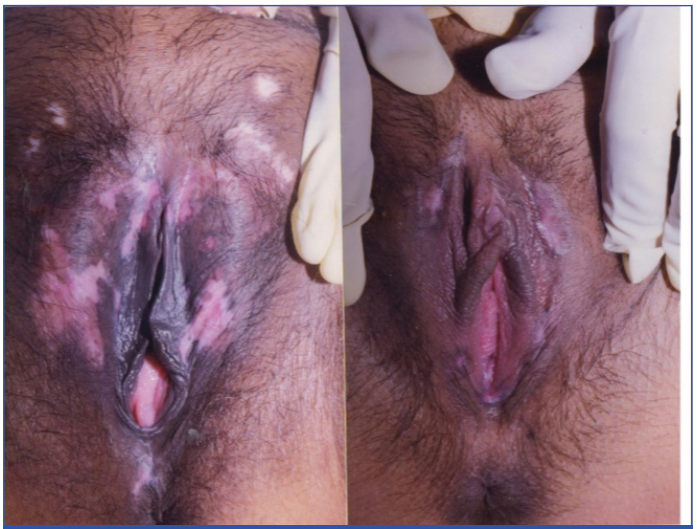
The indicators of safety and tolerability were the immediate and delayed side effects experienced by patients of both study groups as shown in [Table/Fig-4].

DISCUSSION

The comparative evaluation of efficacy and safety of Liquid Nitrogen Cryotherapy as monotherapy with that of Liquid Nitrogen

Characteristics	Group A (n=30)	Group B (n=30)	p-value
Pain/ Stinging sensation	26	24	0.624
Delayed Ulcer healing	4	8	0.361
Secondary infection	-	2	0.309
Hypopigmentation	16	22	0.256
Scarring	-	2	0.309
Neurological symptoms	-	-	-

[Table/Fig-4]: Tolerability assessment in two treatment groups



[Table/Fig-5]: Hypopigmentation after cryosurgery with subsequent reduction in post-inflammatory hypopigmentation

Cryotherapy in combination with topical Podophyllin was carried out in sixty patients suffering from CA. CA is a common sexually transmitted viral disease of the genitalia for which, depending upon the availability, both Cryotherapy and Podophyllin application are the most commonly employed treatment procedures [9].

Since the introduction of Liquid Nitrogen Cryotherapy (boiling point-196°C) into clinical practice by Dr Ray Allington in 1950, it is being commonly used as dermatological treatment modality [12]. It has an advantage over other modalities in treating latent HPV infection because of immune-modulation and in treating bulky warts, grouped lesions and lesions on the hair-bearing areas [18]. In randomized controlled trials using cryotherapy for EGWs, clearance rates of 54–88% and recurrence rates of 21–40% have been reported with monotherapy [1]. The major draw backs are pain, ulceration and requirement of multiple sessions in case of recalcitrant warts. However, the effects of cryotherapy are entirely local, making it the current therapy of choice for pregnant women with multiple warts [15].

Podophyllin has been found to be an effective, safe and non-invasive method for the treatment of superficial CA. In randomized controlled trials, PD monotherapy yields moderate clearance rates of 41–77% and high recurrence rates of 25–70% [1]. The adverse effects to PD therapy can present as acute toxicity, long term toxicity, mutagenicity and carcinogenicity, Reproductive toxicity and local toxicity. Local skin reactions are usually seen as erythaema, tenderness, pruritus, burning, oedema and pain and intense irritation; rarely as erosion, ulceration, scarring and phimosis. Systemic toxicity can occur if PD is substantially absorbed into the body; so its application should be limited to no more than 0.5 ml per session. Systemic side effects may include nausea, vomiting, confusion, renal failure, paresthesias, leukopenia, coma, bone marrow depression, teratogenicity, mutagenicity and death [15]. Thus, it is absolutely contraindicated in pregnancy [1]. PD continues to be used for treatment of CA because of easy availability of treatment [9].

The present study was undertaken to evaluate the clinical effectiveness of combined application of these two procedures in order to assess the possibility of further optimization of the treatment response of these individual treatment methods. The complete response rate and the recurrence rate in the Group B in our study were comparable to Group A as the difference was statistically insignificant. The difference worth mentioning was that the similar results were obtained in Group B with an average 1.2 sessions per patient in comparison to an average of 1.67 sessions per patient in Group A. These findings were consistent with the findings of Sherrard et al., [19]. On searching the available literature, only a few comparative studies regarding the therapeutic efficacy of liquid nitrogen Cryotherapy with or without Podophyllin in treating CA could be found.

As evident from the results, the clearance rate of warts in the urethral meatal and vaginal area is extremely low and the recurrence rate in the urethral meatal and vaginal area is extremely high in our study. Further studies are necessary to determine whether the lower response rate and higher recurrence rate of warts in the urethral meatal and vaginal area correlate with the latent, non-visible intra-meatal and vaginal HPV infection, anatomically difficult to approach locations or pain sensitivity of the mucosa.

The incidence and severity of side effects experienced by the patients in both study groups included mild to moderate pain, delayed ulcer healing, secondary infection, hypopigmentation [Table/Fig-5] and scarring after treatment were comparable which however were not of statistical significance. Moderate to severe pain during treatment and hypopigmentation was noticed in almost all the patients in both study groups and was obviously due to cryotherapy. Secondary infection and scarring was observed in two patients of group B probably because PD increases the tissue necrosis and thus the incidence of side effects. In none of the patients, 48 hours after the procedure, neurological symptoms or haematological and biochemical abnormalities could be detected. So, PD in a dose less than 0.5 ml in single sitting in combination with cryotherapy does not seem to significantly get absorbed systemically so as to produce these side effects.

The requirement of second session in the combined cryotherapy plus PD group was only 20.00% in our study which was significantly (p–value = 0.010) lower than 66.67% of cryotherapy monotherapy group. In other words, in combined therapy group, an average 1.2 sessions was required per patient in comparison to an average of 1.67 sessions per patient in monotherapy group. Thus, the efficacy in terms of response and recurrence rate in a single session is significantly high in group on combination therapy than in group on monotherapy.

Considering the pain during and after application of liquid nitrogen followed by necrosis and blistering after a session of cryotherapy, combination of PD with cryotherapy can decrease the morbidity of the treatment and can shorten the treatment schedule of CA patients.

LIMITATION

The small sample size and inability to investigate the optimal time of contact and intensity of freezing temperature is the main limitation of the study. The intensity of injury caused by cryotherapy was assessed only clinically and hence was an important variable in administration and the results.

CONCLUSION

This study confirms that cryotherapy represents a simple, safe and effective regimen for the treatment of multiple CA which in combination with Podophyllin is more effective as a single session procedure; thereby shortening the treatment regimen although both the study groups had equivalent efficacy.

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