TREATMENT OF CONDYLOMA ACUMINA WITH PODOPHYLLOTOXIN VERSUS COMBINATION THERAPY

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Condyloma acuminata is growing problem due to its resistance to conventional treatment, increased recurrence rate and its relationship with carcinoma. We have designed this study to evaluate the efficacy, adverse effects and immunomadulating effects of podophyllotoxin as a treatment modality of condyloma acuminate as compared to podophyllotoxin plus interferon alpha-1 cream. Podophyllotoxin as monotherapy and its combine[1] ion therapy with interferon alpha-1 cream produced complete response in 40% and 68% while recurrence in 48%> and 20% patients respectively. Topical podophyllotoxin produced pain and inflammation while after its combination with interferon alpha-1 cream. The incidence of adverse effects remained the same. Lymphoblast transformation activity and natural Killer activity were performed for every patient before either of treatment modalities and after only in case of combination thereby.

KEY WORDS: Condyloma acuminate podophyllotoxin, interferon alpha-1 Lymphoblast transformation activity, Natural Killer activity.

INTRODUCTION

Condyloma acuminata or Anogenital warts are said to be sexually transmitted disease of viral aetiology. Human papilloma virus is a double stranded DNA virus belonging to papoviridea family. Recently human papilloma virus has been extensively studied as regard its structure, carcinogenicity, immunohistopathology and host defense against virus. Most genital warts are caused by HR-6 and HPV-16. Most of the times, transmission is by sexual intercourse.

Papilloma viruses are species specific and most types show definite tropism for specific anatomic sites.

HPV-1 causes genital warts', HPV-2 common warts and HPV-6 anogenital warts. The incubation period of condyloma acumionata virus is 1-8 months. In men most common site is penis, paranal area while in females, commons site is vulva. Complications of condyloma aeuminata include rapid enlargement during pregnancy producing obstruction of birth canal and possible rare transformation into cervical dysplasia and carcinoma[2]. HPV infection of female genital tract is also thought to be' a reservoir for most recurrent and treatment[3] resistant condyloma acuminala in sexual partners.

Condyloma acumination can present as hyperplastic cauliflower like lesions, sessile papules or Keratotic verruca vulgarus like lesions.

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Application of 5% acetic acid for 3-5 minutes' maker subclinical lesions as acetowhite Application of 5 % acetic acid for 3-5 minutes' maker subclinical lesions as acetowhite and more prominent under colposcopic examination[4].

Cell medicated immune system is said to play an important role in propagation recurrence and progress of condyloma acuminata. Natural killer activity, production of interferon gamma and interleukin-2 were decreased in patients of condyloma acuminala while suppressor T cells (Leu 2+) were increased[5].

Various treatment modalities including surgery, electro-surgery, cytotoxic, cryotherapy and interferons are available but still effective, safe and curative regimen is lacking.

MATERIALS AND METHODS

Patients were registered for this study at outpatient department and medical laser department of Institute of Dermatology, shanghai Medical University, Shanghai.

Men and women of 15 to 60 years' age in good general health with at least two lesions of condyloma acuminate with a total surface area of 5-100 mm were eligible[2]. Patients with untreated, recurrent or persistent condyloma acuminata were included in this study. Patients who received therapy for condyloma acuminata within two months before registration or who had used interferon alpha for any purpose one month before registration or patients using cytoloxics or immunomadulating drugs were excluded from study.

Altogether 50 patients were registered according to above mentioned criteria and they were further divided into two equal groups of 25 patients each on first come first serve basis.

Natural Killer activity was determined for every patient before treatment and after treatment in combination therapy only according to 5technique by Cauda *et al.,* [5]

The lymphoblast transformation activity was measured for every patient before treatment and after treatment in combination therapy only using a microcullur method according to Amman *et al.,* [6].

0.5% podophyllotoxin solution was supplied as a box of 3ml plastic bottle with applicator. Cream containing 20 miu of recombinant interferon alpha-1 per gram of cream base was prepared by hospital pharmacy according to Vesteman *et al.*[7].

The cream was packed in 10 gms plastic boxes and was stored at temperature of -20°C. The patient was instructed to store this cream below 4°C in refrigerator so as to maintain its activity.

Before treatment, the number shape, and size of condyloma acumminata was recorded for every patient. The sub-clinical lesions were detected by applying 2% gentian violet and treated but not recorded for study purpose. Patients were followed up on weekly basis for first month and then on monthly basis for next two months after treatment. The treatment response at end of lollow up period was classified as complete (90-100% disappearance), partial (50-90% disappearance). Failure (less than 25% disappearance), progressive (Appearance of new lesions during treatment), Recurrence (Appearance of new lesion after treatment). The appropriate standard statistical methods were used to calculate arithmetic mean, standard arrow and P value.

RESULTS

Podophyllotoxin only.

05% Podophyllotoxin solution applied by the patients themselves was analyzed as a treatment modality among 25 patients. Patients in this group had a male female ratio of 60:40% with a mean age of 32.54+1.73 years (Table 1). The average duration of condyloma acuminata was 16.20+3.07 weeks and mean surface area was 20.80+2.64 mm (Table 1). The different distribution sites of condyloma acuminata were, penile 36%, vulvar 44%, perianal 8% and multiple sites 12% respectively (Table 1). The detailed demographic data, clinical characteristics, status of cellular immunity and end point response are given in Table 1.

The status of cellular immunity in this group of patients was determined before treatment only. Mean lymphoblast transformation activity was 16199.96+1848.68 (Table 1) as compared to 19214.34+1235.50 cpm of disease free healthy control group. The difference between lymphoblast transformation activity of disease group before treatment and control group was not significant (P>0.01).

Mean natural killer activity of this group before treatment was 31.21+2.35% (Table 1) as compared to 31.45+2.32% of disease free healthy control group. The difference between natural killer activity of disease group was not significant (P> 0.01) as compared to control group.

Complete cure was seen in 40% patients while the response was partial in 8% and fair in 4% patients with Podophyllotoxin as treatment modality at the end of follow up period (Table 1). None of the patients in this group had failure or progressive responses. The recurrence rate among this group of patients treated with Podophyllotoxin was 48% (Table 1).

The commonest adverse effects observed in this group of patients were pain in 20% and inflammation in 40% patients (Table 1). No other side effects were seen in this group.

Podophyllotoxin plus interferon Alpha-1 Cream.

The combination treatment modality of 0.5% topically applied Podophyllotoxin solution plus recombinant interferon alpha-1 cream was tried as a treatment modality on 25 patients. Baseline demographic data, clinical characteristics, status of cellular immunity and end point response of this group of patients are given in Table 2.

The sex distribution in this group was, males 52%, females 48% while mean age was 37.32+2.10 years (Table 2). The mean duration of condyloma acuminata was 9.08 + 2.00 weeks while mean number of lesions was 12.40+2.59 (Table 2). Penile lesions were 28%, vulvar 32%, perianal 24% and multiple sites 16% (Table 2). The mean surface area of condyloma acuminata in this group was 2 27.64 + 2.59mm (Table 2).

The status of cellular immunity in terms of lymphoblast transformation activity and natural killer activity was assayed before and after completion of treatment. The mean lymphoblast transformation activity before and after treatment was 15145.41 + 1109.65 and 32446.34+1616.40 cpm respectively (Table 2).

The rise in lymphoblast transformation activity after treatment was significant (P< 0.01, Table 2).

The mean natural killer activity before and after treatment was 31.09+1.85 and 53.89+1.88% respectively (Table 2). The rise in natural killer activity after treatment was significant (P<0.01, Table 2).

The complete response in this combination treatment modality was seen in 68%, while partial and fair responses were in 4% and 8% patients respectively (Table 2). None of the patients in this group demonstrated failure or

Table-1: Podophyllotoxin only

Pat No.	Sex	Age (Yrs)	Duration (Weeks)	No.	Site	Area (mm2)	LTA (cpm)	NKA (8)	End point response
1	F	37	48	19	V	33	17580	32.8	Complete
2	M	31	6	11	P	32	11331.28	43.94	Complete
3	M	41	4	16	M	17	29413.3	52.1	Complete
4	F	19	8	5	V	14	32194	21.48	Recurrence
5	F	32	6	9	PA	9	8992.84	23.57	Partial
6	M	30	12	8	P	23	17323.25	25.2	Recurrence
7	M	20	40 -	7	P	50	30287	41.48	Recurrence
8	M	39	48	9	P	38	7621.2	17.57	Partial
9	F	29	3	4	V	12	7506.5	21.3	Complete
10	F	23	4	3	V	13	12922	47.9	Complete
11	M	37	3	3	p	6	33367.1	40.4	Complete
12	M	32	24	20	V	40	24648.9	10.5	Recurrence
13	F	37	12	12	V	48	4076.36	24.9	Fair
14	F	37	12	4	V	6	17148	33.72	Complete
15	M	25	6	3	M	5	10471	25.4	Complete
16	M	40	8	11	V	20	31205.8	27.1	Recurrence
17	F	35	36	6	V	9	9619.5	14.9	Recurrence
18	M	37	8	4	V	32	8840.46	27.98	Recurrence
19	M	25	24	7	P	12	22826.1	43	Complete
20	F	38	4	6	V	24	11072.1	45.3	Recurrence
21	M	59	4	4	p	20	13667.25	38.4	Recurrence
22	F	22	12	5	M	16	5622.85	25.4	Recurrence
23	M	26	48	3	P	7	18392	47.14	Complete
24	M	30	13	3	P	14	13226.22	21.25	Recurrence
25	M	37	12	7	PA	20	5643.8	21.4	Recurrence
N = 25	M (60%) F (40%)	32.45 ±1.73	16.20 ±3.07	7.56 ±0.98	P (36%) V (44%) PA (8%) M (12%)	20.80 ±2.46	16199.96 ±1848.68	31.21 ±2.35	Complete (40%) Partial (8%) Fair (4%) Failure (Nil) Progressive (Nil) Recurrence (48%)

Table-2: Podophyllotoxin plus INF. alpha-1 cream

Pat No.	Sex	Age (Yrs)	Duration (Wks)	No.	Site	Area (mm2)	LTA1 (cpm)	LTA 2 (cpm)	NKA1 (%)	NKA2 (%)	Endpoint response
1	F	24	8	5	V	17	12712.48	25252.2	26.4	48.28	Complete
2	F	36	8	10	M	25	13554.3	29721.54	33.2	62.25	Complete
3	M	32	4	7	P	10	18724.55	41431.91	32.5	46.3	Complete
4	M	32	3	5	P	8	14243.5	29976.34	28.36	60	Complete
5	F	23	1	4	V	42	11160.71	30792.25	21.23	38	Complete
6	M	29	2	4	P	8	15625.22	36292.12	20.17	37.3	Complete
7	M	36	48	10	P	15	11723.2	23558.52	29.4	41.79	Recurrence
8	M	45	8	50	PA	50	12718.12	29225.28	23.2	69.3	Recurrence

9	M	50	24	20	PA	75	6938.72	37223.5	12.9	37	Fair
10	F	25	4	10	V	17	24728.32	47972.51	36.59	59.72	Complete
11	M	38	2	3	P	5	26729.25	32875.62	28.96	53.92	Complete
12	F	37	10	5	V	12	17734.23	21291	39.23	47.5	Complete
13	M	36	2	12	V	12	12472.5	30145	38	61.3	Recurrence
14	F	•34	8	8	V	8	9462.8	43721.52	25.24	51.9	Complete
15	M	42	12	50	PA	100	21890	38411.5	41.24	58.02	Recurrence
16	F	46	3	3	PA	50	27380	34287.32	25.29	52.6	Recurrence
17	M	50	12	8	P	20	17237	22850	19.27	43.5	Partial
18	F	50	12	30	M	82	7341	28253.2	37.5	69.79	Fair
19	F	41	8	12	PA	13	13721.2	48278.52	47.2	59.75	Complete
20	M	44	2	12	PA	26	15756.5	28106.24	31.68	56.25	Complete
21	M	29	4	3	P	6	17287.22	42892.3	46	62.7	Complete
22	F	32	4	6	V	13	15674.3	23856.74	23.8	52.2	Complete
23	M	41	8	9	M	23	13721.25	37850.7	47.13	62.32	Complete
24	M	38	20	20	M	42	6742.16	24330.68	23.4	59.3	Complete
25	F	37	4	4	V	12	13356.75	22562	39.5	56.3	Complete
N = 25	M (52%) F (48%)	37.72 ±2.10	9.08 ±2.00	12.40 ±2.59	P (28%) V (32%) PA (24%) M (16%)	27.64 ±5.15	15145.41 ±1109.65	32446.34 ±1616.40	31.09 ±1.85	53.89 ±1.88	Complete (68%) Partial (4%) Fair (8%) Failure (Nil) Progressive (Nil) Recurrence (20%)

Abbreviations:

F: Female M**:** Male, P**:** Penile, **V:** Vulva, **PA:** Perianal, **Mi:** Mixed, **LT 1:** Lymphoblast transformation activity before treatment, **LT 2:** Lymphoblast transformation activity After treatment. **NKA:** Natural Killer activity before treatment
NKA 2: Natural killer activity after treatment

progressive responses. The recurrence rate among this group was 20% (Table 2). The adverse effects commonly observed in this group were pain in 24% and inflammation in 28% (Table 2).

DISCUSSION

In our study, 0.5% Podophyllotoxin applied by the patient themselves on the lesions of condyloma acuminata, twice daily for three days a week for two weeks, produced a complete response in 40%, partial response in 8%, fair response in 4% and recurrence in 48% patients respectively. None of the patients in this treatment group had failure or progressive responses.

Lymphoblast transformation activity and natural killer activity before treatment with podophyllotoxin were comparable to disease free healthy control group whose data were obtained from file.

Podophyllotoxin produced pain in 20% and inflammation in 40% patients as adverse effects. No other subjective complaints or change in normal laboratory parameters were noted.

Beutner et al[8] reported a recurrence rate of 34% with podophyllotoxin in previously completely resolved condyloma acuminata. Von Krogh[9] reported a cure rate of 49% with self-applied Podophyllotoxin twice daily for three days. Our results are comparable to these studies but our end point response was calculated after a follow up period of three months after completion of treatment.

Podophyllotoxin as monotherapy for treatment of condyloma acuminata is less effective as compared to combination therapies but is more convenient to be applied by patient himself and more economical. Podophyllotoxin is antimitotic drug which in case of condyloma acuminata suppresses the rapid cell division in epidermis so as to retard the growth of exophytic lesions of condyloma acuminata but has nothing to do with cell mediated immunity and host defense against HPV infection. Podophyllotoxin is topically applied strictly on exophytic lesions while subclinical lesions are usually spared which can be important source of recurrences.

The combination therapy of Podophyllotoxin with recombinant interferon alpha-1 cream produced complete response in 68%, partial response in 4%, fair response in

8% and recurrence in 20% patients. None of the patients in this group had failure or progressive response. The recurrence rate of combination therapy of podophyllotoxin with recombinant interferon alpha-1 cream is significantly less ($P < 0.01$) than monotherapy with Podophyllotoxin. Over all cure rate of combination therapy of Podophyllotoxin with recombinant interferon alpha-1 cream is significantly higher ($P<0.01$) than Podophyllotoxin as monotherapy. The combination therapy of Podophyllotoxin with recombinant Interferon alpha-1 cream produced a significant rise ($P<0.01$) in lymphoblast transformation activity and natural killer activity.

This indicates a local and systemic immunomadulating effect of recombinant Interferon alpha-1 cream. May be this factor is contributory to enhanced cure rate and less marked recurrence rate of combination therapy of Podophyllotoxin with recombinant Interferon alpha-1 cream as compared to Podophyllotoxin as monotherapy. Clinical trials regarding combination therapy of Podophyllotoxin with Interferon alpha-1 cream for treatment of condyloma acuminata have yet not been reported.

The combination therapy of Podophyllotoxin with recombinant Interferon alpha-1 cream produced pain in 24% and inflammation in 28% patients as adverse effects. Laboratory parameters remained unchanged in this treatment group.

Combination therapy of Interferon alpha and Podophyllin have been reported as a better treatment modality of condyloma acuminata as compared to Podophyllin alone by Douglas JM et al.[10]. Combination therapies of various ablative procedures with various Interferon preparations and their comparative efficacy, safety, have been scarcely reported in Medical Journals.

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