

A COMPARATIVE EVALUATION OF THERAPEUTIC EFFICACY AND SAFETY OF THE CRYOTHERAPY (LIQUID NITROGEN) WITH TOPICAL 20% PODOPHYLLIN V/S INTRALESIONAL BLEOMYCIN WITH TOPICAL 5% PLACENTREX GEL IN THE TREATMENT OF CONDYLOMA ACUMINATA

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ABSTRACT

Background: Condyloma acuminata is a common sexually transmitted disease of sexually active adults caused by HPV having variable response to the different available therapies and none of them have proved to be uniformly effective as recurrences are common.

Objective: A randomized, single blinded, paralleled group, intention to treat prospective study was conducted not only to compare the two treatment modalities but also to determine the efficacy and safety of drugs under study.

Materials and Methods: 60 cases of clinically diagnosed condyloma acuminata were randomly divided into two equally matched groups (n=30). Group-I, patients were treated with a combination of cryotherapy (liquid nitrogen) with topical 20% podophyllin and Group-II, patients were treated with a combination of intralesional bleomycin with topical 5% placentrex gel. Evaluation criteria included assessment of lesion response, patient's response, duration of response, recurrence rate and safety. Photographic assessment at baseline, 2, 4, 8, 12 and 24 weeks was done.

Results: 289 condylomas were treated in total (n=60), 175 (60.55%) Group-I and 114(39.4%) in Group-II. 49 patients completed the study, 24 treated in Group-I and 25 in Group-II. By intention to treat, lesional clearance rate at 24 weeks in Group-I was 80% as compared to 83.33% in Group-II. The clinical efficacy of combination therapy in Group-II was higher as compared to Group-I but there was no statistically significant difference between both the groups (p >0.05). The side effects evaluated in this study were mild and transient and they were assessed using a 4 point clinical score (0=absent, 1=mild, 2=moderate, and 3=severe).

Conclusion: In this comparative study Intralesional bleomycin with 5% placentrex gel was found to be more effective although both treatment modalities have good potential for treatment of condyloma.

Keywords: Anogenital warts, Liquid Nitrogen, Combination therapy, Intralesional injection, Topical application.

INTRODUCTION

The genital warts [syn-Condyloma Acuminata and anogenital warts] were known since antiquity, particularly in the Greek and Roman era [1]. The term Condyloma acuminata is derived from ancient Greek, meaning "a round swelling adjacent to the anus." It is a sexually transmitted disease caused by Human Papilloma Virus [HPV] and there are more than 35 types of HPV that infect the genital tract [2]. The incubation period of venereal warts ranges between 3 weeks to 8 months, average being 2.8 months [1]. In India, it is about 3.4 months and its range is between 10 days to 13 months [3]. HPV infection is probably the most common sexually transmitted disease worldwide. Approximately 20 million Americans are currently infected with it and about 6 million people become newly infected each year [4]. Various treatments have been used for genital warts [5] and there is no specific therapy available to cure HPV at present [6]. Different treatment options include various topical therapies (salicylic acid, cantharidin, podophyllotoxin, 5-fluorouracil or bleomycin), newer immunomodulatory treatments (imiquimod or interferons), physical destructions (surgical excision, cryotherapy, electrodesiccation or laser therapy) [7, 8, 9] and homoeopathic therapy [10]. Liquid Nitrogen (cryotherapy) produces tissue necrosis by freezing and it also stimulates specific immune responses i.e. immunomodulatory action of T lymphocytes directed against the rest of the viable warty tissue [7, 8, 9].

Podophyllin is a crude extract derived from the May apple plant (podophyllum peltatum or podophyllum emodi). Podophyllum resins contain cytotoxic lignin that binds to microtubules and induces tissue necrosis by blocking cell mitosis [8, 9]. Studies have shown that local oedema produced by liquid nitrogen (cryotherapy)

allows better surface penetration of podophyllin, hence, enhancing the overall effect [8, 9].

Intralesional bleomycin has been used in the treatment of condyloma since 1960 [9]. It selectively inhibits DNA by binding to DNA; leading to single strand scission in DNA and elimination of pyrimidine and purine bases [8, 9, 11]. Thus, it interferes with the cell cycle at the M and G2 phase. It is also believed to have an effect on protein synthesis, which is thought to cause biochemical changes leading to apoptosis and necrosis of keratinocytes [8, 9, 11].

Placentrex exerts significant Immunotropic action occurring both at cellular and humoral level as seen in human and animal models [12], it increases IgG and IgM level at the humoral level and total lymphocytes at cellular level thus increasing the immunity in the body [12, 13]. It has been found that the placentrex extract acts through HP axis and in need helps the body to produce natural cortisol which acts on phospholipase-A2 and secondly, it also inhibits the pathway of COX and LOX which ultimately results in blockade in the production of prostaglandins and leukotriens [12, 13].

In spite of many available studies on Cryotherapy, podophyllin and bleomycin in treating Condyloma little research has been done to compare their treatment efficacies in combination forms to treat condyloma.

Objective: The purpose of this study was to compare and evaluate the therapeutic efficacy and safety effects of combination therapies of Cryotherapy (Liquid Nitrogen) with topical 20% podophyllin and

intralesional bleomycin with topical 5% placentrex gel in Condyloma acuminata. Primary end points / outcomes of the study were complete clearance of wart and recurrence of warts at 2 weeks, 4 weeks, 8 weeks, 12 weeks and 24 weeks. Secondary end points/ outcomes were adverse effects and complications.

METHODS AND MATERIALS

This investigation (trial) was conducted as a comparative, single blinded, randomized, parallel grouped, intention to treat prospective study to assess the therapeutic efficacy and safety effects of cryotherapy (Liquid Nitrogen) with 20% podophyllin versus bleomycin with 5% placentrex gel for twelve weeks. This study had the approval of the Institutional Ethical Committee. Patient's written informed consent was taken before the commencement of the study. The study drugs were allocated among the patients randomly as Group-I and Group-II (Figure 1). This simple randomization had been achieved by using a Random Number Table, each random number was sealed in opaque envelope and then accordingly patients were allocated into either Group-I or Group-II after opening of these sealed envelopes by person other than the investigators. Patients were evaluated at day 0, then at every 2, 4, 8, 12 and 24 weeks for clinical examination and other parameters by the two independent observers who were dermatologists but not the investigators. They also counted number, size of the lesion and took photographs of lesions at the first and subsequent visits for record purposes. All patients underwent serological testing for hepatitis B surface antigen, VDRL and HIV antibodies.

Inclusion Criteria

60 patients (30 in each group) of clinically diagnosed cases of Condyloma acuminata, aged between 15-70 years, were selected

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Exclusion Criteria

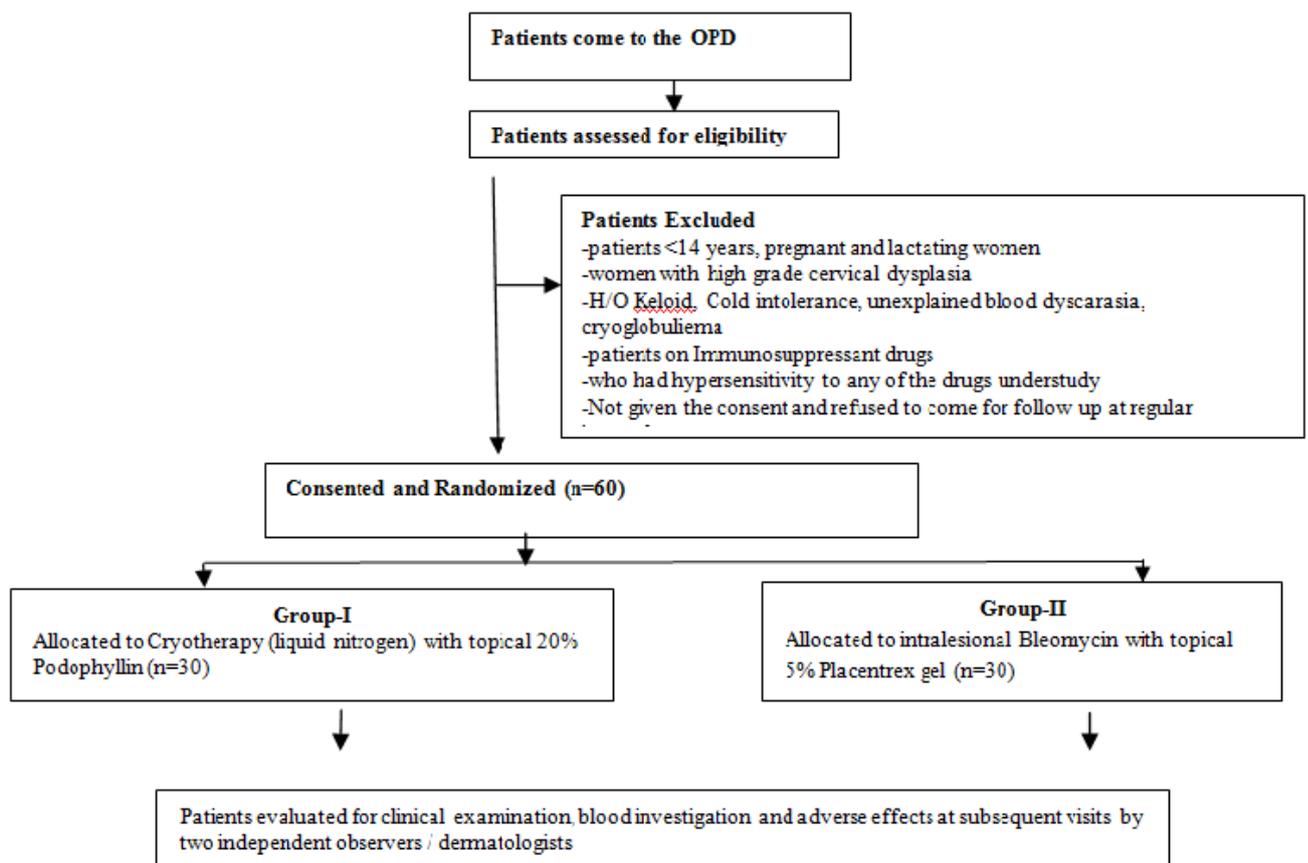
- Patients who had a history of keloid, hepatic, renal and thyroid disorder.
- Pediatric age group, pregnant and lactating women.
- Women with high grade cervical dysplasia.
- HIV and leprosy.
- Presence of obvious internal genital wart.
- Patients who were already taking medication (like study drugs, oral contraceptive pills and corticosteroids).
- Cold intolerance and cryoglobuliema.
- Patients of unexplained blood dyscrasia and on immunosuppressant drugs.
- Patients sensitive to the study drugs were excluded from the study.

Patients who failed to complete the treatment regimen or who did not return for a 12 weeks follow up visit after warts clearance were considered non-compliant and were excluded from final analysis.

Study Drugs and Treatment

Group-I patients were treated with a combination therapy of Cryotherapy (liquid nitrogen) with topical 20% podophyllin.

Group-II patients were treated with a combination of Bleomycin (intralesional) with topical 5% placentrex gel.



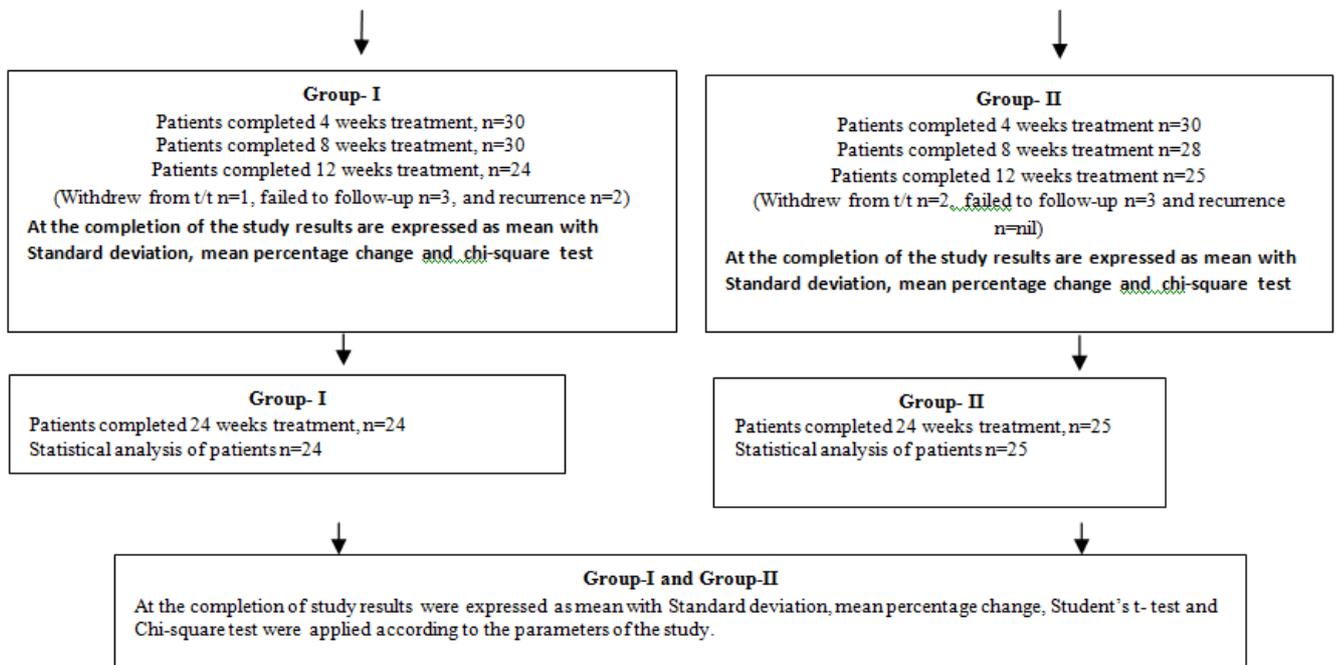


Figure 1: Shows Study Design (Flowchart)

Study Methodology

Group-I, enrolled patients (n=30) were treated with two to three, 20-30 second rapid freeze slow thaw cycles using liquid nitrogen spray technique with a spray gun using nozzles of suitable sizes to freeze the warts tissue in segments of 1cm. Freezing was carried up to 5mm margin of clinically normal skin surrounding the lesion with a spray gun held perpendicular to the wart at a distance of 2 mm [14] and for every large lesion this freezing margin was 10 mm until the ice ball formation was seen. By sequential overlapping method, complete condylooma was covered with liquid nitrogen. After complete thawing, surrounding area was protected by applying liquid paraffin, from an over flow of 20% podophyllin in tincture benzoic solution which was applied on the lesion (Condylooma acuminatum) every two weeks [15] till complete resolution occurred. Patient was instructed to wash off the application of podophyllin after three hours of application each time it was applied. Application was limited to less than 0.5 ml or less than 10 cm² area per session to decrease the risk of systemic absorption [16].

Group-II, enrolled patients (n=30) were treated by dissolving the contents of injection bleomycin in 15 ml of 1% lignocaine (each vial of bleomycin contains 15 IU of bleomycin sulphate IP) such that each individual lesion received 0.1 ml of IU/ml of bleomycin. Not more than a total dose of 2 ml of bleomycin was administered per session to any patient [17]. This treatment was performed every two weeks until resolution occurred. The injection was given intralesional taking all aseptic precautions directly into the warts raising a wheal using 0.5 cc tuberculin syringe (gauge 30 1/2) taking precaution not to inject more than 1 unit per individual wart and maximum dose injected was two units per treatment session. One unit was injected into 5 cm² and two units into the 10 cm² in one session. Area more than 10 cm² was injected in the following session till resolution of the lesion occurred. After injection, bleomycin ice water soaks were given for 10-15 minutes, two times per day for four days. After drying the lesion, the patient was instructed to apply placentrex gel

topically at night till the lesion resolved. The treatment was performed every two weeks until the lesions resolved.

Both the therapies were applied for a maximum of five treatments and two weeks apart till complete resolution occurred. Prior to the start of therapies, each patient had his/her warts measured at baseline and with each return visit including a post treatment follow up that was twelve weeks apart from the last treatment taken.

Drugs were applied under aseptic conditions, observing universal precautions at each treatment session. Affected areas/ lesions were also evaluated for adverse drug events during and after application of these drugs to avoid serious consequences. Patients were kept under strict observation for 24 hrs to watch immediate complications. Along with the drugs under study, all the patients were administered analgesics and anti-inflammatory drugs (except corticosteroids) for 7-10 days, according to prescribed guidelines to take care of pain and inflammation due to therapy. During the study period, patients were instructed to avoid or have only protected sexual intercourse and to refer their partners to the clinic for evaluations.

Efficacy Assessments

The effects of drugs on the subjects were assessed by observing the decrease in the size of lesion, either partial or complete from the baseline. Lesions were measured by the formula: Length X Width. Lesion responses were categorized as follows:

Complete response (CR) - 100 %

Partial response (PR) - 50-99%

No response (NR) - < 50 %

The secondary efficacy assessments were done using investigator global assessment scale (IGAS) and patients global assessment scale (PGAS) during each follow up visits.

Table 1: Shows Patient's Demographic Data

Characteristics	Group-I	Group-II	p-value
Number	n=30	n=30	
Age (years):	27.60 ± 9.64	29.56 ± 9.06	
Median (range)	(14 - 60)	(19 - 62)	<i>p</i> >0.05
Sex: n (%) Male	19 (63.33)	24 (80.0)	-
Married	10 (33.33)	14 (46.67)	
Female	11 (36.67)	6 (20.0)	
Married	9 (30)	5 (16.67)	
Sex ratio	1.172:1	4:1	-
Marital status (ratio)	1.72:1	1.71:1	-
Heterosexual (%)	66.67	80.0	-
Source of acquisition of warts: Community Sex Workers (%)			-
	53.33	53.33	
Most common - Classical type (cauliflower) (%)	66.67	53.33	-
Location of Warts: n (%)	Coroneal Sulcus and Glans penis	Coroneal Sulcus and Glans penis	-
Commonest site involved in male:			
Commonest site involved in female:	Labia majora and inner thigh	Labia majora inner thigh	
Commonest other STD in	14	12	<i>p</i> >0.05
Male:	Balanoposthitis	Balanoposthitis	
Female:	Vaginal Discharge	Vaginal Discharge	
Number of Warts: Mean ± SD (range)	7.93 ± 7.69	6.66 ± 3.88	<i>p</i> >0.05
Upto 5	(1 - 25)	(1 - 19)	
6-10	50%	73.33%	
>10	40%	13.33%	
	10%	13.33%	
Duration of Warts:			
Mean ± SD (months)	6.8 ± 6.11	9.51 ± 16.11	<i>p</i> >0.05
95% CI	4.43- 9.16	3.50- 15.53	
Estimated total area of warts	1204 cm ²	755 cm ²	
Mean ± SD	40.13 ± 37.12	25.16 ± 31.49	<i>p</i> >0.05
95% CI	26.27-53.99	13.40- 36.92	
Median (range)	24 % (n=17)	27.55% (n=22%)	
• <5 cm ²	38.46% (n=9)	43.84 (n=6)	
• 5-10 cm ²	37.54% (n=4)	28.61% (n=2)	
• > 10 cm ²			

* Student's t test

Safety Assessments

During each visit occurrence of adverse events were assessed and recorded keeping a note to treatment compliance. The assessment of adverse events was done on the basis of their nature; intensity and outcome relationship with the study drugs. Safety laboratory assessments were done wherever required.

Statistical Analysis

Data were analyzed as per protocol. The data were expressed as mean ± standard deviation (SD) and mean percentage change. Other statistical tests were applied like student's t test and Chi-square test according to the parameters of the study. Values of **p*<0.05, ***p*<0.01, ****p*<0.001, *****p*<0.0001 were considered statistically significant.

RESULTS

Demography

Of 60 eligible patients who gave informed written consent, 49 patients completed their treatment course and were analysed for efficacy and those not completing the study were excluded. 81.67% showed complete response, 6.67 % cases showed relapse and only 11.67% drop outs were present at the end of study (Figure 1). Baseline characteristics and baseline values of different parameters of both the groups were compared at the start of therapy and was found statistically similar (*p* >0.05). It was also observed that 43.33% of cases were associated with other sexually transmitted diseases. Incidence of the warts was more in males as compared to females (Table 1). In Group-I, three patients (10%) did not come for follow-up and one patient (3.33%) refused to continue with the understudy drug while two patients had recurrence of the lesions (left the treatment midway) at 12 weeks. While in Group-II three

(10%) patients failed to come for follow-up and two (6.67%) refused to continue with the drug under study at 12 weeks (Figure 1).

Efficacy Analysis

Group-I

Cryotherapy (Liquid Nitrogen) with topical 20% podophyllin resulted in significantly therapeutic effects in patients at completion of 2 weeks (30%), 4 weeks (40%), 8 weeks (60%) and 12 weeks (60%) as complete clearance of lesion. While at 24 weeks, 80% patients had shown complete clearance (Figure 2 A-D, Table 2).



Figure 2 Photographic assessment for Cryotherapy (Liquid nitrogen) with 20% Podophyllin at Visit 1, Visit 2, Visit 3 and Visit 4

Group-II

Bleomycin with Placentrex gel in Group-II resulted in significant responses in patients at completion of 2 weeks (73.33%), 4 weeks (86.67%), 8 weeks (83.33%) and 12 weeks (70%) as complete clearance. At 24 week 83.33% patients had shown complete clearance while none had shown partial response (Figure 3 A-D, Table 2).

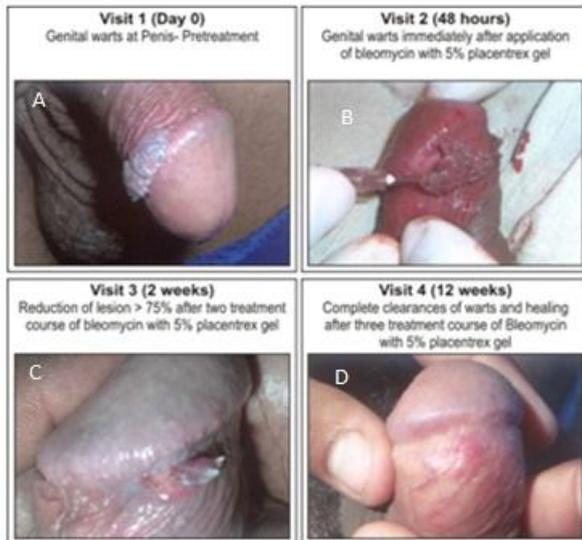


Figure 3 Photographic assessment for Intra-Lesional Bleomycin with Placentrex Gel at Visit 1, Visit 2, Visit 3 and Visit 4

Safety Assessments

Both groups exhibit similar safety profiles. In Group-I, early side effects generally seen were burning (46.67%, n=14), stinging (46.67%, n=14), edema (36.67%, n=11), pain (23.33%, n=7),

bleeding (16.67%, n=5) and irritation (6.67%, n=2) (Table 3). It was observed that eighteen patients (60%) had developed burning, stinging and edema simultaneously, pain and irritation in six while bleeding and pain occurred in three patients. These side effects were mild in nature and resolved within few days (1-2 days). Dhar SB et al [14] observed that pain occurred by 12% with cryotherapy (monotherapy) that was more than combination of cryotherapy with podophyllin in our study. While late side effects were secondary infections (16.67%), desquamation (33.33%), hypopigmentation (63.33%) and scar (6.67%) in Group-I (Table 3). Hypopigmentation was less as revealed by Dhar SB et al (91%) [14], while scar formation was also common with cryotherapy but other studies did not mention their incidence. Both discoloration or hypopigmentation and scarring are less in our study. Adlatkhah H et al [18] reported that severe complication was 4.55% with cryotherapy while with no such complication had been seen in Group-I.

In Group-II, common side effects were seen as pain (70%, n=21), burning (66.67%, n=20), bleeding (56.67%, n=17), edema (43.33%, n=13) and irritation (16.67%, n=5) with combination of bleomycin with topical 5% placentrex (Table 3). It was observed that ten patients (33.33%) had developed burning, pain and edema simultaneously. Bleeding and pain in five patients (16.67%), while burning and stinging occurred in five (16.67%). It had been seen that mild pain (70%) was more seen with combination therapy as compared to AlGhamdi KM et al (60%) [19], Golchia J et al (45.3%) [20] and Dhar SB (5%) [14] respectively. Delayed side effects were edema, erythema and ulceration more frequently seen than secondary infections, desquamation, hypopigmentation and scar. Erythema (16.67%) was very less as revealed by Golchia J et al. (90.4%) [20] and hypopigmentation / discoloration (10%) was also very less as disclosed by AlGhamdi KM et al (13.33%) [19], Golchai J et al (90.4%) [20] and Dhar SB et al (46%) [14] respectively. Severe complication was not seen in Group-II while Adalatkah H et al reported it was by 6.81% (3/44) with intralesional Bleomycin [18].

Table 2: Shows Comparison of Efficacy of Combination Therapy in Both Groups

Time interval	Groups	Total no. of cases	Complete response	% age	Comparison	X ²	p value
48 hrs.	I	30	0	0	I & II	-	-
	II	30	0	0			
2 weeks	I	30	9	30	I & II	9.611	< 0.001
	II	30	22	73.33			
4 weeks	I	30	12	40	I & II	12.12	<0.001
	II	30	26	86.67			
8 weeks	I	30	18	60	I & II	5.041	<0.05
	II	30	25	83.33			
12 weeks	I	30	18	60	I & II	0.182	>0.05
	II	30	21	70			
24 weeks	I	30	24	80	I & II	0.182	>0.05
	II	30	25	83.33			

X²-Chi-square test (with Yates correction)

DISCUSSION

Condyloma acuminata is a common sexually transmitted disease showing high level of recurrence in spite of treatment and impair quality of life by impacting the self esteem. In the present study, the combination therapy showed more clearance of warts compared to monotherapy of cryotherapy by Adalatkah H et al at 6 weeks (complete response of warts at hands and feet with cryotherapy was 68.2%, p< 0.001) [18]. In a randomized clinical trial, Stone KM et al observed that monotherapy of podophyllin and cryotherapy at 12 weeks showed complete response as 41% (p<0.0001) and 79% (p<0.0001) [21] and another trial by Layegh P et al at 12 weeks, in genital warts also showed 26% and 41% complete response with monotherapy of podophyllin and cryotherapy respectively [22]. It had been seen that complete response was less observed with the

use of monotherapy in these clinical studies (Adalatkah H et al, Stone KM et al and Layegh P et al [18, 21, 22] as compared to the

combination therapy in Group-I. Partial clearance of lesion with this combination (in Group-I) was less as compared to those disclosed by Stone KM et al with podophyllin (58.73%, n=37/63) but more than cryotherapy (20.93%, n=18/86) [21]. While recurrence observed with this combination was very less (6.66%) as compared to those disclosed by Layegh P et al (26% and 41% with monotherapy of podophyllin and cryotherapy)[22], Tabrizi SN et al (40%, with cryotherapy) [23] and Guntar J (30%, with podophyllin) [24] and Wiley DJ et al (60%, with podophyllin) [25].

In Group-II, it had been observed that complete response at 4 weeks was more (86.67%) while it was less at 12 weeks and 24 weeks (71% and 83.33% respectively) as disclosed by AlGhamdi KM et al

(46.6%, 90% and 86.6% respectively with monotherapy of bleomycin (applied as multipuncture technique in periungual warts) [19] while complete response at 24 weeks was slightly less as revealed by Golchai J et al (88.4%, with combination therapy of intralesional bleomycin plus lignocaine) [20] after 8 weeks. It had been observed that complete response (Table 2) was less as revealed by Dhar SB et al (94.9%, in a randomized controlled trial of intralesional Bleomycin in the cutaneous warts after 8 weeks) [14] and Adalatkah H et al (86.4%, $p < 0.001$ complete response after 6 weeks therapy of intralesional bleomycin (monotherapy) in the treatment of warts of hands and feet) [18]. AlGhamdi KM et al observed that recurrence rate with intralesional bleomycin was 6.67% (2/15) [19] while with combination therapy of bleomycin with topical 5% placentrex gel did not show recurrence.

Comparison of observations of the treatment groups

Efficacy of Combination

It had been observed that at 2, 4 and 8 weeks, combination therapy of bleomycin with placentrex gel (Group-II) showed highly significant ($p < 0.001$) response in the form of complete clearance of warts as compared to cryotherapy with topical podophyllin (Group-I). While at 12 and 24 weeks, Group-I cases showed lesser clearance of lesion as compared to Group-II (Table 2) but recurrence rate of warts was 6.67% in Group-I while none in Group-II at 24 weeks.

Table 3: Shows Comparison of Safety profile of Combination Therapy in Both Groups

Appearance of Side Effects	Side Effects	X ²	D.F.	R.R
48 hrs	Burning	1.697	1	0.7
	Stinging	4.929	1	2.8
	Pain	11.317	1	0.33**
	Bleeding	8.684	1	0.294**
	Irritation	0.6469	1	0.4
2 week	Edema	0.0694	1	0.844
4 week	Secondary infections	0.1442	1	1.667
8 week	Erythema	0.1307	1	0.8
	Desquamation	2.39	1	2.5
12 week	Ulceration	0.282	1	0.769
24 week	Hypopigmentation	19.697	1	6.597***
	Scar	0.0018	1	1.042

X²-Chi-square test (with Yates correction)

Safety profile of Combination

The most common side effects seen at 48 hours in Group-II were pain, burning sensation and edema which were more as compared to Group-I, while irritation and bleeding were more in Group-I as compared to Group-II.

The most common side effects seen after 48 hours of therapy in Group-I were bullae (40%), which were not seen in Group-II. While desquamation and secondary infection were more in Group-I as compared to Group-II but ulceration and erythema were less as compared to group II (Table 3).

It had been observed that delayed complications were secondary infections (at 4 weeks), desquamation (at 8 weeks), hypopigmentation and scar formation (at 24 weeks) was relatively more in Group-I as compared to Group-II. While secondary infections were mild and localized, none of the patients had developed severe infection (Table 3). These were managed by prescribing a course of antibiotics for five to seven days. There was no significant change in laboratory parameters.

CONCLUSIONS

Combination of drugs as shown in our study proved that the synergistic effects of drugs have better outcomes as compared to monotherapy in improving the cure rate and reducing the recurrences. Both the groups had shown comparable efficacy and safety profile as a treatment by showing better efficacy, minimum recurrence rate and lesser side effects due to synergistic or additive actions of the medicines in the combinations, thus both the therapies

have a good potential to be offered as treatment for genital warts. Combination therapy of intralesional bleomycin with 5% placentrex gel had better efficacy as complete warts clearance with negligible recurrence rate, rapid action and lesser side effects (like secondary infections, discoloration, scar formation and lack of severe complications). Intralesional bleomycin with 5% placentrex is well tolerated by the patients. This combination therapy does not require sophisticated equipments making it more suitable for the treatment of warts even in the remote areas. We can treat more patients with this kind of combination where monotherapies have failed without referring the patients to the tertiary care hospitals. This will further limit the spread of disease in the society as well.

LIMITATIONS

Limitations of this study were the small sample size and exclusion of patients having intramucosal lesions in the anogenital region. Larger sample size studies are required to confirm our results.

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DECLARATION

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REFERENCES

- Oriel JD. Natural history of genital warts. Br J Vener Dis 1971; 47(1):1-13.
- de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur Hausen H. Classification of papillomaviruses. Virology 2004 Jun; 324(1):17-27.
- Ganguli DD, Sundharam JA, Bhargava NC. A Clinico-epidermiological study of genital warts. Indian J Dermatol Venereol Leprol 1983; 49(4):153-7.
- Centre for Disease Control. Genital HPV infection. Available online at <http://www.cdc.gov/std/HPV/STDFact-HPV.htm> [Last accessed on Nov18th, 2013 at 9.50pm]
- Lipke MM. An armamentarium of wart treatments. Clin Med Res 2006 Dec; 4(4): 273-93.
- Desai S, Wetten S, Woodhall SC, Peters L, Hughes G, Soldan K. Genital warts and cost of care in England. Sex Transm Infect 2011 Oct; 87(6): 464-8.
- Thappa DM editor. Essentials in Dermatology. 2nd Editor. New Delhi: Jaypee Brothers Medical Publishers (P)Ltd, 2009.
- Lopaschuk CC. New approach to managing genital warts. Can FamPhysician 2013 Jul; 59(7): 731-6.
- Husseinzadeh N. Basic Therapeutic Principles and the Strategy in the Management of the External Anogenital Warts (Condylomas): A Review: J Clin Gynecol Obstet 2013 June; 2(1): 1-9.
- Das CN. Evidence Based Homoeopathy in Treating Condyloma Acuminatum-A prospective and interventional study. Asian J Pharm Clin Res 2013; 6(suppl (1):124-6.
- Kwok CS, Gibbs S, Benette C, Holland R, Abbott R. Tropical treatments for coetaneous warts. Cochrane Data Syst Rev 2012; 9:1-180.
- Ansari KU, Gupta N, Bapat SK. An experimental and clinical evaluation of immunomodulating potential of human placentrex extracts. Indian J Pharmacol 1994; 26(2): 130-2.
- Shibasaki T, Odagiri E, Shizuma K et al. Corticotrophin release factor like activity in human placentrex extracts. J Clin Endocrinology Metabol 1982; 55:384-6.
- Dhar SB, Rashid MM, Islam A, Bhuiyan M. Intralesional bleomycin in the treatment of cutaneous warts: a randomized clinical trial comparing it with cryotherapy.

- Indian J Dermatol Venereol Leprol 2009 May-Jun;75(3):262-7.
15. Forcier M, Musacchio N. An overview of human papillomavirus infection for the dermatologist: disease, diagnosis, management, and prevention. *Dermatol Ther* 2010 Sep-Oct; 23(5):458-76.
 16. Kirby P, Dunne A, King DH, Corey L. Double-blind randomized clinical trial of self-administered podofilox solution versus vehicle in the treatment of genital warts. *Am J Med* 1990 May; 88(5):465-9.
 17. Amer M, Diab N, Ramadan A, Galal A, Salem A. Therapeutic evaluation for intralesional injection of bleomycin sulphate in 143 resistant warts. *J Am Acad Dermatol* 1988;18(6):1313-6.
 18. Adalatkah H, Khalilollahi H, Amini N, Bazargani SH. Compared therapeutic efficacy between intralesional bleomycin and cryotherapy for common warts: A randomized Clinical Trial. *Dermatology online Journal* 2007; 13(3) Available online at <http://www.escholarship.org/uc/item/62g03mj> [Last accessed on Nov18th, 2013 at 10.00pm]
 19. AlGhamdi KM, Khurram H. Successful treatment of periungual warts with diluted bleomycin using translesional multipuncture technique: a pilot prospective study. *Dermatol Surg* 2011 Apr; 37(4):486-92.
 20. Golchai J, Mobarhan Vaghe Karegar M. Therapeutic evaluation of intralesional of injection of Bleomycin Sulfate in the treatment of resistant warts. *Medical J Islamic Repub Iran* 1995; 8(4): 233-6.
 21. Stone KM, Becker TM, Hadgu A, Kraus SJ. Treatment of external genital warts: a randomized clinical trial comparing podophylline, cryotherapy and electrodesiccation. *Genitourin Med* 1990;66(1):16-9.
 22. Layegh P, Pezeshkpoor F, Malekshah PET, Shakeri MT. Cryotherapy versus podophylline in the treatment of genital warts. *Iranian J Obstet, Gynecol and Infert* 2008;10(2):133-8.
 23. Tabrizi SN, Garland SM. Is cryotherapy Treating or infecting? *Med J Australia* 1996; 164(5)263-4.
 24. Gunter J. Genital and perianal warts: new treatment opportunities for human papillomavirus infection. *Am J Obstet Gynecol* 2003 Sep; 189(3 Suppl):S3-11.
 25. Wiley DJ, Douglas J, Beutner K, Cox T, Fife K, Moscicki AB, Fukumoto L. External genital warts: diagnosis, treatment, and prevention. *Clin Infect Dis* 2002 Oct 15;35(Suppl 2):S210-24.