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ORIGINAL ARTICLE

Comparison of Clinical Efficacy of 0.1% Intralesional Bleomycin Solution and 0.05% Intralesional bleomycin Solution in Patients with Warts

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ABSTRACT

Background: Warts are the hard, hyperkeratotic benign growths over the skin caused by human papilloma virus. It is one of the common skin conditions presented to the outpatient department. Various treatment options are available with variable success but sometimes it is resistant to treatment due to its depth in the dermis and relapsing nature.
Aim: To compare clinical efficacy of 0.1% intralesional bleomycin solution and 0.05% intralesionalbleomycin solution in the patients with warts.
Study settings & design: Experimental, Dermatology, LUMHS Jamshoro
Duration: 1st January 2018 to 30th June 2018
Methods: 90 patients with persistent common warts were enrolled. Patients were examined and number of warts located on right and left hand, feet and leg of each patient were categorized in two groups as right sided group and left sided group respectively. The two concentrations of bleomycin were randomly adminitered to either right sided and left sided warts which are called, the lesion **A** in which 0.1% IL bleomycin solution was injected and the lesion **B** in which 0.05% IL bleomycin solution was injected respectively. The Response of the both therapies was assessed by measuring the size of warty lesions on 6thweek. Then patient was advised to report at the end of 14th week to observe any recurrence in the treated lesions and to assess the final clinical efficacy.
Results: - Mean age of patients was 25.36 ± 6.09 years. There were 50(55.56%) male and 40(44.44%) females. Clinical efficacy as per operational definition i.e. Complete disappeared or >50% regression in size of warts with no recurrence was significantly high in lesion A than lesion B [93.3% vs. 68.9%; p=0.0005]. Regarding number of warts in patients, 86.1% of the warts were cured in lesion A while 64.9% were cure in lesion B. The difference was statistically significant.
Conclusion: - Our results support that 0.1% IL Bleomycin is more effective in the treatment of viral warts as compared to 0.05% bleomycin.
Keywords: Common Warts**,** Intralesional, Bleomycin treatment

INTRODUCTION

Viral warts are a common dermatological problem. Patients with warts present not only to the dermatologist but also to family physicians and general surgeons.1The estimated European countries prevalence of warts is between 3 and 20 percent.2 In a study conducted in Iran the prevalence of warts was 15 percent in age group 12-16 years and 25 percent of the people enrolled in the study gave history of warts in the past[3].

Warts are hyperkeratotic, hard, papules and sometime nodules with a cauliflower like projections on the skin but may have flat or spiky surface. These are mainly present on soles of feet and palms and face but may be found anywhere on the body[4]. Cutaneous warts are caused by human papillomavirus (HPV).5Diagnosis of warts is mainly clinical.6Variousmodalities are available and being practiced for the treatment of warts. These include topical preparations like Salicylic acid solutions, Imiquimod cream, tretinoincream and topical zinc sulfate solution. Interalesional 5-Flourouracil and vitamin D are also being practiced with variable results. Among systemic options, oral zinc sulfate, cimetidine and parentral Bacillus Calmette-Guérin (BCG) vaccination are available. Minor procedures include electrocautery with curettage and cryotherapy[7].

Bleomycin has not been a commonly practiced modality in the treatment cutaneous warts in our country, although it is being practicedfor this purpose in various regions of the word since 1970s.8Many studies have been published worldwide on the use of intralesionalbleomycin for the treatment of warts with efficacy of 14% to 99%.9Previous studieson 0.1% IL bleomycin solution that were conducted in neighbor countries show 94.9% cure 13% recurrence, 5% severe pain 63% dyspigmentation.10

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The study on 0.05% IL bleomycin solution shows 86.4% cure 8.6% side effects and less than 3% recurrence following the therapy[11].

Rationale of the study is that there no research has ever been conducted on national or international level to compare the clinical efficacy of 0.1% IL BLEOMYCIN solution and 0.05% IL BLEOMYCIN solution for the treatment of common warts . This study is designed to compare the clinical efficacy of the both concentration of the bleomycinsolution. If the results of study reveal that 0.05% bleomycin solution is equal or superior in efficacy than 0.1% bleomycin solution, then it was recommended to treat the common warts.

The objective of the study was to compare the clinical efficacy of 0.1% intralesional bleomycin solution and 0.05% intralesional bleomycin solution in the patients with warts.

OPERATIONAL DEFINITIONS:

Common warts: Presence of scaly rough spiny papules/nodules on any cutaneous surface.

Efficacy: The clinical efficacy was evaluated at 14th week from the 1st injection given into the wart. It was said positive if equal or more than 50% regression in size of wartand no recurrence.

The positive clinical efficacy to therapy was graded as follows

Very good: More than 80-100% regression in size or complete disappearance of the wart with no recurrence at the end of 14 week.

GOOD: More than 50%-79% regression in size of the wart with no recurrence at the end of 14 week.

No efficacy: Less than 50% regression in size of the wart and/or presence of recurrence of wart observed on the end of 14th week.

Recurrence: Reappearance of wart and/or increase in size of wart after initial regression during therapy.

Hypothesis: There is difference in clinical efficacy of intralesional 0.1% bleomycin solution and 0.05% bleomycin solution in treatment of common warts.

PATIENTS & METHODS:

Settings: Out Patient Department of Dermatology, Liaquat University Of Medical and Health Sciences, Jamshoro/Hyderabad, Sindh, Pakistan This study was conducted from 1st January 2018 to 30thjune 2018.

Sample size: The previous study on 0.1% IL bleomycin solution that was conducted in Bangladesh show 94.9% cure 13% recurrence (P1=87%) .8 The study on .05% IL bleomycin solution that was conducted in Iran shows 86.4% cure and less than 3% recurrence following the therapy (P2=97%).11 The sample size was estimated 90 cases n=90 (1-β =80%, α=5%).

Sample technique: Non probability consecutive sampling

Inclusion criteria: Participants having persistent common warts of minimum 3months duration having size minimum 3mmor more, Distribution of the common warts would be bilateral/ unilateral on extrimities, Minimum number of warts will not be less than 2, Patient willing to take part in study with valid consent on the procedure and followup and male and female participants of age between 12 to 40 years.

Exclusion criteria: Patients having warts on genital area and/or face, already diagnosed cases of systemic lupus erythematosus (SLE), Systemic sclerosis, Raynaud's disease/phenomenon, Pregnant, lactating patients, Patients having hypersensitivity to the content of injection, all patients using any other therapy for warts, non cooperative & prisoners

Study design: Experimental

Data collection: The valid consent was taken from the patient meeting the inclusion criteria, the cases was advised not to use any other therapy for the warts to minimize the confounding. Patient was evaluated at first visit as per our perfroma. A brief history along with a graphical map of the warts was made for each patient, the number, location, size, type and duration of wart was noted on it. The lesions was equally divided, then named as A and B. The lesion **A** in which 0.1% IL bleomycin solution was injected and the lesion **B** in which 0.05% IL bleomycin solution was injected .The both A and B groups were observed for response of therapy at the end of every 2nd week . Maximum three injections would be given by the 2 week interval, upto end of 4th week. The Response of the both therapies was assessed by measuring the size of warty lesions on 6thweek. Then patient was advised to report at the end of 14th week to observe any recurrence in the treated lesions and to assess the final clinical efficacy.

Ethical approval: Approval from ethical review board of Liaquat University of Medical And Health Sciences Jamshoro/ Hyderabad was taken before starting the study.

Study medications and methods of administration: The required study material was arranged by researcher. Injection Bleomycin (INJ.BLENICO 15IU) is available in the form of 15 mg powder contained in a voil. Injectable stock solution was prepared by adding 5 ml distilled waterwith strength of 3mg/1mL. 2% lignocaine was further added to obtain required concentration of solution which was made as under with tuberculin syringe.

- ✓ *0.1% IL BLEOMYCIN SOLUTION=1ml stock solution+2ml Lignocaine 2%*
- ✓ *0.05% IL BLEOMYCIN SOLUTION=0.5ml stock solution+2ml Lignocaine 2%*

The injection without lignocaine can be safely storedfor2 months at temp. 4-8°C.[12]

Skin area involving wart was prepared by cleaning with alcohol swab. Before injecting the medication the excess callus over the wart was removed by superficial paring by scalpel blade size 15. The bleomycin solution was injected intralesionally in the wart till blanching of the area occurs. The quantity of the solution injected varied with the size of warts: 0.2ml was injected in the warts up to 5 mm of size, 0.5ml was injected in 6mm-10 mm size and 1.0ml was administered in more than 10 mm size of lesion. The maximum volume delivered at one time was 3ml in an area and maximum 1ml of injection was given to a single wart at a time.

Data Analysis: All data was collected using a two pager proforma, then checked and edited was cleaned accordingly. At the end of study final data was analyzed with Statistical Package for the Social Sciences (SPSS) version 24.0. The variables like age, duration of warts and size of warts was evaluated by descriptive statistics mean and Standard deviation .The variables like gender, number of warts, site of warts, recurrence and efficacy of each solution was analyzed with frequencies/percentages. The

clinical efficacy of 0.1% IL bleomycin solution and 0.05% IL bleomycin solution was compared by applying Chi-square test. The stratification was done with regarding to age, gender, and size of wart and duration of wart to control effect modifier/ confouder by applying chi square test. A *p*-value≤0.01 was considered as statistical significance.

RESULTS

In this study, 90 patients with persistent common warts were enrolled. Patients were examined and number of warts located on right and left hand, feet and leg of each patient were categorized in two groups as right sided group and left sided group respectively.. Each patient received both treatments on his/her warts. The two concentrations of bleomycin were randomly administered d to either right sided and left sided warts which are called, the lesion **A** in which 0.1% IL bleomycin solution was injected and the lesion **B** in which 0.05% IL bleomycin solution was injected respectively.

Mean age of patients was 25.36 ± 6.09 years. Average duration of warts and size of warts are also reported in table 1. There were 50(55.56%) male and 40(44.44%) females.Table-1 Distribution of warts according to location is shown is shown in Figure-1. There were 556 warts was found in 90 cases. The average number of warts in lesion A was 3.11±0.68 and in lesion B was 3.07±0.72 as presented in table 2.

Table -1: Descriptive statistics of characteristics & gender distribution of the patients

Descriptive Statistics		Age (Years)	Duration of warts (months)	Size of Warts(mm)
Mean		25.36	7.0	5.61
Std. Deviation		6.09	1.58	1.75
95% Confidence Interval for Mean	Lower Bound	24.08	6.67	5.24
	Upper Bound	26.63	7.33	5.97
95% Confidence Interval for Mean	Lower Bound		2.97	2.92
	Upper Bound		3.25	3.22

Male	Female	**Total**
50(55.56%)	40(44.4%)	**90(100%)**

Figure 1: Location of warts

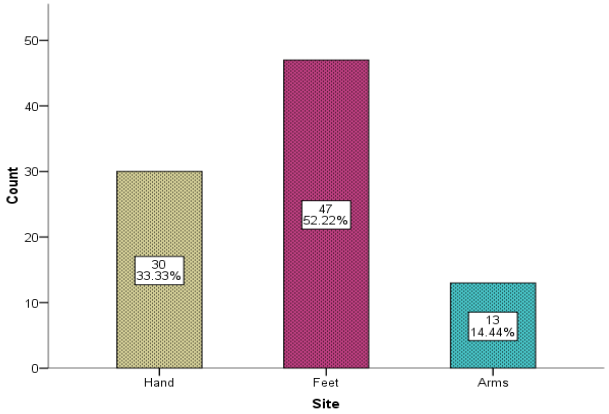

Figure-2: Figure-2: RESPONSE OF TREATMENT AT THE END OF 14TH WEEK FROM 1ST INJECTION GIVEN INTO WARTS n=90 patients with 556 warts: [Lesion A=280 warts and Lesion B 276 warts]

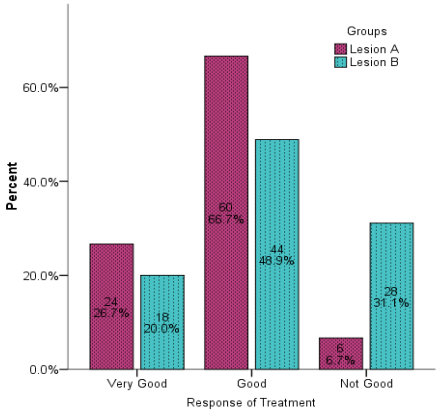

Figure 3: Recurrence status

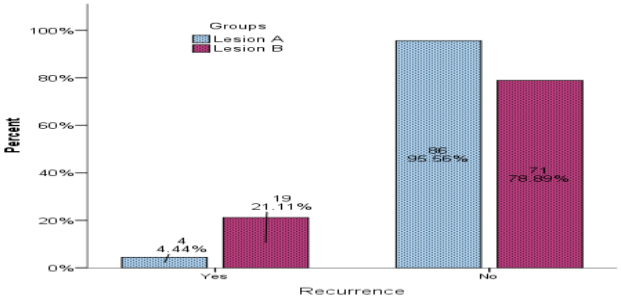

Table 2: Mean number of warts according to (lesion a and lesion b) n=90

Descriptive Statistics	Number of Warts	
	Lesion A	**Lesion B**
Number of warts (m)	**280**	**276**
Mean	3.11	3.07
Std. Deviation	0.68	0.72

Table 3: Comparison of clinical efficacy of 0.1% intralesional bleomycin solution and 0.05% intralesional bleomycin solution in the patients with common warts

Clinical Efficacy	Lesion A	Lesion B	Total
Effective*	84(93.3%)	62(68.9%)	146(81.1%)
Not Effective	6(6.7%)	28(31.1%)	34(18.9%)

Chi-Square= 17.55 p=0.0005, *Effective:** Complete disappeared or >50% regression in size of warts with no recurrence, ***Not Effective#*** *<50% regression in size of warts*

Table 4: Comparison of number of warts cured and not cured between lesions

Number of Warts [cured/not cured]	Lesion A m=280	Lesion B m=276	Total m=556
No of warts cured	241(86.1%)	179(64.9%)	420(75.5%)
Number of warts not cured	39(13.9%)	97(35.1%))	16(24.5%)

Chi-Square= 33.86; p= 0.0005, m= Number of warts,

Response of treatment at the end of 14th week from 1st injection given into warts is shown in figure 2. Most of the response in lesion A was good and very good. Clinical efficacy as per operational definition i.e. Complete

disappeared or >50% regression in size of warts with no recurrence was significantly high in lesion A than lesion B [93.3% vs. 68.9%; p=0.0005] as shown in table 3. Regarding number of warts in patients, 86.1% of the warts were cured in lesion A while 64.9% were cure in lesion B. The difference was statistically significant as present din table 4. Recurrence status was also high in lesion B than lesion A [21.11% vs.4.44% p=0.0005]. Figure-3
Stratification analysis was performed with respect to age gender, average size of warts, site of warts and duration of warts and observed that cure rate of warts was significantly high in lesion A than lesion B for all type of stratification are extensively explained and presented in table 5.

Table 5: comparison of clinical efficacy of bleomycin between groups in the patients with common warts (with regard to stratification of age, gender, size of wart, location of wart & duration of wart)

	Clinical Efficacy	Lesion A	Lesion B	P-Value
< 30 years of Age	Effective	64(94.1%)	49(72.1%)	0.001
	Not Effective	4(5.9%)	19(27.9%)	
>30 years of age	Effective	20(90.9%)	13(59.1%)	0.015
	Not Effective	2(9.1%)	9(40.9%)	
Males	Effective	48(96%)	34(68%)	0.0005
	Not Effective	2(4%)	16(32%)	
Females	Effective	36(80%)	28(70%)	0.024
	Not Effective	4(10%)	12(30%)	
Size of wart 3-6mm	Effective	50(89.3%)	38(67.9%)	0.004
	Not Effective	6(10.7%)	18(32.1%)	
Size of wart 7-9mm	Effective	34(100%)	24(70.6%)	0.001
	Not Effective	0(0%)	10(29.4%)	
Location of warts (Hands)	Effective	28(93.3%)	18(60%)	0.002
	Not Effective	2(6.7%)	12(40%)	
Location of warts (Feet)	Effective	44(93.6%)	33(70.2%)	0.003
	Not Effective	3(6.4%)	14(29.8%)	
Location of warts (Arms)	Effective	12(92.3%)	11(84.6%)	0.539
	Not Effective	1(7.7%)	2(15.4%)	
Duration of warts < 6 weeks	Effective	46(95.6%)	32(66.7%)	0.0005
	Not Effective	2(4.2%)	16(33.3%)	
Duration of warts >6 weeks	Effective	38(90.5%)	30(71.4%)	0.026
	Not Effective	4(9.5%)	12(28.6%)	

Effective: *Complete disappeared or >50% regression in size of warts with no recurrence*
Effective : *<50% regression in size of warts*

DISCUSSION

Warts are one of the common cutaneous infectious diseases caused by human papilloma virus (HPV). Human papillomavirus (HPV) penetrates the epidermal cells and causeshyperproliferation of keratinocytes leading to the formation of hard, rough, papule mostly projects through the skin but sometimes have a plane top surface. More than 100 HPV types are recognized, with affinity for different body sites. It predominantly affects palms and soles, genitalia and face but other skin areas may get infected. Various therapeutic modalities are available for the treatment of wartsbut none of these is 100% effective hence combination therapies have also been practiced.[2]Intralesional bleomycin is relatively a novel treatment option for the management of viral warts. Various researchers have reported good efficacy of intralesional bleomycin in the treatment of warts with cure rates of 14% to 99%.9Bleomycin is frequently used as an antitumor drug. It also has antibacterial and antiviral activity. It acts on the cells and makes bonds with deoxyribonucleic acid (DNA) leading to excision and loss of pyrimidine and purine bases attached with it.12 The bleomycin gets inactivated in the body by hydrolase enzyme present in all the body tissues. This enzymeis scarcely present in the skin. After intralesional injection, a significant amount of the drug remains active locally to act on the warts. So small concentration of drugs usually effective for the treatment of warts.12To compare clinical efficacy of 0.1% intralesional bleomycin solution and 0.05% intralesional bleomycin solution in the patients with warts, 90 patients of both gender age between 12-40 years with persistent common warts were enrolled in this study. Depending on the location of warts these patients were divided into two groups, right sided wart group and the left sided warts group. There were 556 warts was found in 90 cases. We included patients from 12-40 years. Maximum numbers of patients were 21-30 years of age, with mean age 25.36 ± 6.09 years. 25.36 ± 6.09 year. There are relatively less mass population-based studies available regarding the prevalence of non-genital warts. Prevalence of viral warts is highly variable among different regions, age groups, and periods of time. A large population-based study done in US showed 0.84% prevalence of warts.13 In another study done in Russia prevalence rates of warts was 12.9%.14 Children and young adults showed high incidence of warts. A study estimated school population in UK showed prevalence 12% in 4- to 6-year-olds kids.15 Similarly supportive evidence was found in a study done in Australia where 24% of 16- to 18-year old people had history of warts.16 Warts are found commonly at the hands and feet, the sites which are more prone to trauma and injuries where there are increased chances of inoculation of virus into epidermis. Walking barefoot increases the chance of contact with virus from other infected people. In an observational study, 27% prevalence on feet was reported in people talking shower in a communal washroom and 1.3% that shared the changing room.17 Butchers and meat handlers are at increased risk of developing warts on their hands. One cross-sectional survey based on prevalence of warts in different

occupational groups found abattoir workers reported 33% prevalence, butchers had 34%, engineering fitters had 20%, and office workers showed 15% prevalence of warts.18In our study 33.3% warts are found on hands, 52.2% on feet and 14.4% on arms.

Gibbs done a systematic review on many published researches and didn't find any consistent evidence regarding the effectiveness of intralesional bleomycin for the treatment of warts.19,20 Most of the studies have shown that bleomycin is an effective treatment modality among two-thirds of the cases with mild side effects.9 In this study, intralesional bleomycin showed greater efficacy for the treatment of warts in lesion A than lesion B. We found most of the response in lesion A was good and very good. Clinical efficacy as per operational definition i.e. Complete disappeared or >50% regression in size of warts with no recurrence was significantly high in lesion A than lesion B [93.3% vs. 68.9%; p=0.0005]. Regarding number of warts in patients, 86.1% of the warts were cured in lesion A while 64.9% were cure in lesion B. Recurrence status was also high in lesion B than lesion A [21.11% vs.4.44% p=0.0005]. In our study, 93.3% palmo-plantar warts got cured which is higher than 87% cure rate done in a study by Salk and Douglas.21In a study done by Olson, the resolution of plantar warts was observed in 18 out of 25(72%) patients treated with intralesional bleomycin versus 5 out of 21 (27%) patients treated with placebo.22 Olson used a dermo-jet which can result in very small quantity of bleomycin injected inside the warts due to scattering of the drug which may be a reason of relatively low efficacy in his study.22 In another study done by Hayes and O'Keefe, 78% efficacy was reported which is much lower than this study, but lower concentration of bleomycin was administered in that study.23Bremner found intralesional bleomycin was effective in 63% of 142 warts in 24 patients which is again less than the present study.24 Shelly and Shelly in a study reported cure rate of 92%.25 The reason of very high efficacy may be due to a different technique in which bleomycin was administered through multiple punctures made in the lesion using a bifurcated vaccination needle.

CONCLUSION

Our study support our hypothesis that there is difference in clinical efficacy of intralesional 0.1% bleomycin solution and 0.05% bleomycin solution in treatment of common warts. Bleomycin treatment does not require any special equipment or setup, it has short course of therapy reducing patient time and low recurrence rate. 0.1% IL Bleomycin is reported to be a relatively effective treatment modality for curing viral warts in our study. Treatment has good safety profile as well as a high cure rate of more than 90%. Side effects are few and rare. More randomized and double-blind studies of adequate sample size are required to further establish safety and effectiveness of IL bleomycin in the management of viral warts.

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