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Original Article

Efficacy and safety of cryotherapy and clobetasol propionate ointment (0.05%) in treatment of localized plaque psoriasis: A randomized controlled trial

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Abstract

Background Psoriasis is a chronic, immune-mediated and genetic based dermatoses, characterized by accelerated cell proliferation of keratinocytes and by the inflammation that results in parakeratotic scales. Treatment may be topical or systemic. Use of clobetasol propionate, a synthetic glucocorticoid with high power, is already known and widely used. Cryotherapy is the application of intense cold to cause tissue necrosis by rapid freezing.

Objective We sought to compare the efficacy and safety of cryotherapy and clobetasol propionate ointment (0.05%) in treatment of localized plaque psoriasis.

Methods A total of 74 patients (37 patients in each group) were included in the study. Patients in group A were subjected to cryotherapy with liquid nitrogen. Patients in group-B were subjected to 0.05% clobetasol ointment. The lesions were assessed four weeks after starting treatment by using Visual Analogue Scale.

Results In group-A mean age of the patients was 30.3±8.1 and in group-B 25.3±9.7 years. There were 22 males (59.5%) in group-A and 15 males (40.5%) in group-B while 15 females (40.5%) in group-A and 22 females (59.5%) in group-B. Cryotherapy was efficacious in 19 patients (51.4%) and clobetasol was efficacious in 33 patients (89.2%). The difference between two groups was statistically significant ($p \leq 0.001$). Similarly, clobetasol group was safer than cryotherapy ($p=0.002$). Outcome of VAS at 4 weeks in group-A vs. group-B was as follows: Complete 9 (24.3%) vs. 25 (67.6%), moderate 10 (27%) vs. 8 (21.6%) and mild 18 (48.7%) vs. 4 (10.8%).

Conclusion This study shows that clobetasol propionate ointment (0.05%) is significantly more effective and safer as compared to cryotherapy in the treatment of localized plaque psoriasis.

Key words
Localized plaque psoriasis, cryotherapy, clobetasol, efficacy and safety.

Introduction

Psoriasis is a chronic, immune-mediated systemic disease with preferential skin involvement. The most common clinical variant is plaque-type psoriasis, characterized by well demarcated, erythematous plaques with adherent silvery scales present particularly over the extensor surfaces and scalp. Genetics are an important component in the etiology of psoriasis. Most genome wide linkage analysis have suggested HLA-Cw6 to be the susceptibility alleles.[1] Although psoriasis occurs worldwide but its prevalence varies among

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different ethnic groups. In UK it is found that prevalence of psoriasis has increased over a 15-year period from 2.3% in 1999 to 2.8% in 2013.[2] Approximately 7.5 million Americans are affected by psoriasis, resulting in a prevalence of 2% to 4% in the United States.[3] There are a wide range of therapies available for the treatment of psoriasis but none of them can completely cure the disease. Topical corticosteroids are universally used in the management of localized plaque psoriasis mainly due to their immunosuppressive and anti-inflammatory properties.[4] Clinical efficacy of clobetasol is well established in the treatment of plaque psoriasis.[5] In a double-blind, multicenter trial in 134 patients with localized, plaque psoriasis, the efficacy of clobetasol propionate ointment (0.05%) was found to be 90%.[6] Cryotherapy is the application of intense cold to cause tissue necrosis by rapid freezing. It has many advantages being rapid, easy and safe with little or no pain.[7] Cryotherapy to treat psoriasis was first evaluated in 1987 by Scoggings who reported a response rate of 67-80% in 35 patients.[8] Later in 1999 Abd El Aziz El Taweel *et al*. conducted a study to determine the efficacy of cryotherapy in small plaque psoriasis. The study group comprised of 50 patients with chronic plaque psoriasis. Ages ranged from 13 to 67 years and plaque sizes from 1 to 5 centimeters in diameter. Thirty-one patients (62%) showed complete 6 resolution, nine (18%) had moderate resolution, five (10%) had mild resolution and five others had no resolution. Efficacy of cryotherapy in treatment of small plaque psoriasis was found to be 60%.[9] Generally, the improvement was better in younger patients and in patients with smaller lesions.

The rationale of study this study is to compare the efficacy and safety of cryotherapy and clobetasol propionate ointment (0.05%) in treatment of localized plaque psoriasis. This study will provide us the latest information regarding efficacy and safety of cryotherapy vs. clobetasol propionate ointment (0.05%) in treatment of localized plaque psoriasis. Long term therapy with topical corticosteroids can lead to skin atrophy, striae and systemic adverse effects like diabetes and hypertension. Cryotherapy is not associated with such adverse effects and has many advantages being rapid, easy and safe with little or no pain.

Methods

This randomized controlled trial was conducted in Department of Dermatology, Lady Reading Hospital, Peshawar from April 2019 to October 2019 over period of six months. Data was collected by non-probability convenience sampling technique. The sample size calculation was done by WHO sample size calculation formula. A total of 74 patients (37 patients in each group) were included in the study. Patients of either sex, any age, clinically suggestive of chronic plaque psoriasis presenting to both outpatient and inpatient departments were enrolled in the study. Patients already on topical or systemic therapy for psoriasis and patients with known hypersensitivity to the drugs/therapies used were excluded from the study. The study was conducted after getting approval from hospital ethical and research committee. All patients attending Dermatology OPD of Lady Reading Hospital Peshawar and meeting the inclusion criteria were included in the study. The purpose and benefits of the study was explained to the patients and they were assured that the study is done purely for data publication and research purpose and a written informed consent was obtained. All patients were subjected to detailed history and clinical examination and were randomly allocated into two groups by lottery method. In each group single psoriatic plaque of same size (1-5 cm) with severe erythema, induration and scales

were selected for treatment. Patients in group A were subjected to cryotherapy with liquid nitrogen. Cryotherapy was performed with a cryogun held perpendicular to the lesion at a distance of 1-2cm. Freezing time ranged from 9 to 15 seconds depending upon the size of plaque. In cryotherapy four sessions were done at weekly intervals. Patients in group-B were subjected to 0.05% clobetasol ointment applied daily for 4 weeks. The lesions were assessed four weeks after starting treatment by using Visual Analogue Scale. In which following parameters were observed 1) erythema 2) induration 3) scaling. Complete resolution: absence of erythema, induration and scaling. Moderate resolution: light pink, slight thickening and rare scale. Mild resolution: red, moderate thickening and defined scales. Therapy in each group was considered successful if there is Complete or Moderate resolution at 4 weeks after starting the treatment. Safety of a therapy was measured in terms of its side effects like blister formation, skin atrophy and pigmentary changes. Treatment was considered safe if there was no blister formation, no skin atrophy and no pigmentary changes. All the observations, including Visual Analogue Scale was conducted under supervision of a single expert dermatologist having minimum of five years' experience. All of the above information including name, age, and gender were recorded in a pre-designed proforma. Exclusion criteria was followed to control confounders and bias in study results. The statistical analysis was performed using statistical package for social sciences (SPSS version 20). Qualitative variables were gender, efficacy and safety and visual analogue scale. Quantitative variables were size and number of lesions. Mean±standard deviation was calculated for continuous variables like age of the patient. Chi square test was applied to compare the efficacy and safety in two groups and p value of less than or equal to 0.05 was considered as significant. Effect modifiers like age, gender, size and number of lesions were addressed through stratification. Post stratification Chi square test. P value ≤0.05 was taken as significant.

Results

A total of 74 patients (37 patients in each group) were included in the study Patients in group A were subjected to cryotherapy with liquid nitrogen. Patients in group-B were subjected to 0.05% clobetasol ointment. In group-A mean age of the patients was 30.3±8.1 and in group-B 25.3±9.7 years. There were 22 males (59.5%) in group-A and 15 males (40.5%) in group-B while 15 females (40.5%) in group-A and 22 females (59.5%) in group-B. Cryotherapy was efficacious in 19 patients (51.4%) and clobetasol was efficacious in 33 patients (89.2%). The difference between two groups was statistically significant (p≤0.001). Similarly, clobetasol group was safer than cryotherapy (p=0.002). Outcome of VAS at 4 weeks in group-A vs 76 group-B was as follows: Complete 9 (24.3%) vs 25 (67.6%), moderate 10 (27%) vs 8 (21.6%) and mild 18 (48.7%) vs. 4 (10.8%). Mean number of lesions in group-A were 38.9±18.9 in group-A and 42.2±19.7 in group-B. Mean size of lesion in group-A was 2.6±0.9cm while in group-B 3.2±0.7cm. Stratification for age, gender, size of lesion and number of lesions was also carried out.

Discussion

Psoriasis is characterized by well-circumscribed, scaly erythematous plaques due to infiltration of inflammatory T-cells producing cytokines in

Table 1 Number of lesions.

Number of lesions	*Group-A (Cryotherapy)*		*Group-B (Clobetasol)*	
	No.	*%*	*No.*	*%*
5-40	19	51.4	21	56.8
≥ 41	18	48.6	16	43.2
Total	37	100.0	37	100.0
Mean±SD	38.9±18.9		42.2±19.7	

Table 2 Distribution of patients.

Distribution of patients by	*Group-A (Cryotherapy)*		*Group-B (Clobetasol)*	
	No.	*%*	*No.*	*%*
Age (Years)				
≤ 25	13	35.1	17	46.0
26-45	24	64.9	20	54.0
Mean±SD	30.3±8.1		25.3±9.7	
Gender				
Male	22	59.5	15	40.5
Female	15	40.5	22	59.5
Efficacy				
Yes	19	51.4	33	89.2
No	18	48.6	4	10.8
Chi square=12.678; P value≤ 0.001				
Safety				
Yes	21	56.8	33	89.2
No	16	43.2	4	10.8
Chi square=9.867; P value=0.002				
VAS				
Complete	9	24.3	25	67.6
Moderate	10	27.0	8	21.6
Mild	18	48.7	4	10.8
Chi square=16.661; P value< 0.001				

Table 3 Distribution of patients by size of lesion (cm).

Size of lesion	*Group-A (Cryotherapy)*		*Group-B (Clobetasol)*	
	No.	*%*	*No.*	*%*
1-3	29	78.4	24	64.9
4-5	8	21.6	13	35.1
Total	37	100.0	37	100.0
Mean±SD	2.6±0.9		3.2±0.7	

skin lesions. Psoriasis most frequently affects the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal cleft, glans penis, and nails which will have a significant negative impact on the quality of life. Even there is no cure for psoriasis, but it is effectively controlled by various therapeutic options used alone or in combination.[10]

Plaque psoriasis is one of the most common forms of psoriasis which doesn't have a complete cure. Topical modalities are the mainstay for treatment of limited chronic plaque psoriasis. These include keratolytics, salicylic acid, corticosteroids, anthralin, photochemotherapy and calcipotriol alone or in combination with topical steroids.[11] Safe, effective, and economical long-term treatment and maintenance choices are required for managing chronic nature of psoriasis and to improve the quality of life. The anti- psoriatic effect of salicylic acid and clobetasol propionate were individually reported in a number of studies.[12]

Table 4 Stratification for age with regard to efficacy.

Age (Year)	*Group*	*Efficacy*		*Total*	*P value*
		Yes	*No*		
≤ 25	Group-A	7	6	13	0.035
	Group-B	15	2	17	
	Total	22	8	30	
26-45	Group-A	12	12	24	0.005
	Group-B	18	2	20	
	Total	30	14	44	

Table 5 Stratification for gender with regard to efficacy.

Gender	*Group*	*Efficacy*		*Total*	*P value*
		Yes	*No*		
Male	Group-A	13	9	22	0.021
	Group-B	14	1	15	
	Total	27	10	37	
Female	Group-A	6	9	15	0.003
	Group-B	19	3	22	
	Total	25	12	37	

Table 6 Stratification for size of lesion (cm) with regard to efficacy.

Size of lesion	*Group*	*Efficacy*		*Total*	*P value*
		Yes	*No*		
1-3	Group-A	17	12	29	0.007
	Group-B	22	2	24	
	Total	39	14	53	
4-5	Group-A	2	6	8	0.006
	Group-B	11	2	13	
	Total	13	8	21	

There are very few publications on the use of cryotherapy in the treatment of psoriasis. We performed an evaluation to determine its efficacy in small plaque psoriasis. We selected 63 patients who had a clinical diagnosis of chronic plaque-type psoriasis and for each patient we evaluated two psoriatic plaques of almost the same size and severity on similar areas of the body. One plaque was sprayed with

Table 7 Stratification for number of lesions with regard to efficacy.

Number of lesions	*Group*	*Efficacy*		*Total*	*P value*
		Yes	*No*		
5-40	Group-A	11	8	19	0.049
	Group-B	18	3	21	
	Total	29	11	40	
≥ 41	Group-A	8	10	18	0.002
	Group-B	15	1	16	
	Total	23	11	34	

Table 8 Stratification for age with regard to safety.

Age (Year)	*Group*	*Safety*		*Total*	*P value*
		Yes	*No*		
≤ 25	Group-A	9	4	13	0.197
	Group-B	15	2	17	
	Total	24	6	30	
26-45	Group-A	12	12	24	0.005
	Group-B	18	2	20	
	Total	30	14	44	

Table 9 Stratification for gender with regard to safety.

Gender	*Group*	*Safety*		*Total*	*P value*
		Yes	*No*		
Male	Group-A	15	7	22	
	Group-B	14	1	15	0.068
	Total	29	8	37	
Female	Group-A	6	9	15	
	Group-B	19	3	22	0.003
	Total	25	12	37	

liquid nitrogen every other day for two weeks and the other plaque was untreated as a control. Complete resolution of the plaque occurred in four patients (6.35 %), mild to moderate resolution was evident in 19 cases (30.1 %), and no improvement occurred in 40 patients (63.5 %). Only one complication, superimposed infection, occurred. Cryotherapy mediates mild resolution of plaques by inducing normal re-epithelization following the physical destruction of the lesions via a reverse Koebner phenomenon. Our findings suggest that cryotherapy is safe to use in the treatment of small- plaque psoriasis but that its efficacy is limited.[7]

In a study, Jarratt *et al.* demonstrated that

Table 10 Stratification for size of lesion (cm) with regard to safety.

Size of lesion	*Group*	*Safety*		*Total*	*P value*
		Yes	*No*		
1-3	Group-A	18	11	29	
	Group-B	22	2	24	0.013
	Total	40	13	53	
4-5	Group-A	3	5	8	
	Group-B	11	2	13	0.026
	Total	14	7	21	

Table 11 Stratification for number of lesions with regard to safety.

Number of lesions	*Group*	*Safety*		*Total*	*P value*
		Yes	*No*		
5-40	Group-A	13	6	19	
	Group-B	18	3	21	0.191
	Total	31	9	40	
≥ 41	Group-A	8	10	18	
	Group-B	15	1	16	0.002
	Total	23	11	34	

treatment of the plaque psoriasis is an important part of psoriasis management. A new and unique formulation of clobetasol propionate 0.05% may provide advantages over the currently available formulations through easy application to hard-to-reach areas and the ability to deliver a fixed dose of corticosteroid. Subjects were randomized to receive either clobetasol propionate 0.05% (n=60) or vehicle spray (n=60) twice daily for 4 weeks, followed by a 4-week treatment-free follow-up period. Efficacy evaluations at all visits included assessment of scaling, erythema, plaque elevation, pruritus, and overall disease severity. Success rates for each of the signs and symptoms evaluated, as well as for the overall disease severity assessment, were significantly in favor of clobetasol propionate (P<0.001). The additional 2 weeks of treatment from weeks 2 to 4 increased the number of cleared subjects from 2% to 25%; treatment success was still in favor of clobetasol propionate (P<0.001) at week 8 (4 weeks post- treatment). No treatment-related serious adverse events occurred during the course of the study. Mild application site burning/ stinging was the most common

treatment- related adverse event, with similar frequency and severity for both active and vehicle groups. There were no reports of skin atrophy, telangiectasia, folliculitis, or hypothalamus-pituitary-adrenal axis suppression. Overall, clobetasol propionate 0.05% administered was effective and safe in reducing scaling, erythema, plaque elevation, and overall disease severity and demonstrates durable clinical response up to 4 weeks after treatment end.[13]

The use of topical corticosteroid preparations in psoriasis is well established with clobetasol propionate, the highest potency topical steroid available for use in patients with psoriasis.[14]

In current study, safety of cryotherapy and clobetasol propionate ointment (0.05%) in treatment of localized plaque psoriasis was found to be 51.4% and 89.2% ($p<0.001$), respectively. Similarly, safety of cryotherapy and clobetasol propionate ointment (0.05%) was 56.8% and 89.2%, respectively. Our findings are comparable with the study of Torsekar and Guatam (2017) and Goldberg *et al.* (1991).[5,6]

Conclusion

In conclusion, clobetasol propionate ointment (0.05%) is significantly more effective and safer as compared to cryotherapy in the treatment of localized plaque psoriasis.

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