Efficacy and Safety of Topical Podophyllin 5% Ointment in Patients with Mild Plaque-Type Psoriasis

Khalifa E.Sharquie*, Adil A.Noaimi **,Wesal K. Al-Janabi***

ABSTRACT:

BACKGROUND:

Psoriasis is a common chronic condition of the skin that is resistant to many therapies. There is a need for the development of novel non-steroidal topical drugs for the treatment of psoriasis.

OBJECTIVE:

To assess the efficacy and safety of topical podophyllin 5% ointment in patients with mild plaque-type psoriasis.

PATIENTS AND METHODS:

Sixty two patients with mild plaque-type psoriasis were enrolled in this study. They were divided into 3 groups: GroupA (21patients)were treated with podophyllin 5% ointment every other day, while Group B(20patients)were treated with clobetasol propionate 0.05%ointment twice daily and 21 patients in Group C were treated with Vaseline twice daily for 8 weeks as a control group. Efficacy was evaluated every 2 weeks for 8weeks using Psoriasis Area and Severity Index (PASI) score and relapse was recorded after cessation of treatment in those patients who achieved good response during 8 weeks follow up period.

RESULTS:

A total of 62patients were 44(70.9%) males and 18(29.0%) females, with: male: female ratio 2.3:1. Their ages ranged from 18-65 (37.5±12.9) years. Their baseline PASI score ranged from 1.2-9(5.2±2.4).

At the end of 8 weeks of therapy : no statistically significant difference in PASI reduction between Group A(66.3±20.7) and Group B(68.1±34.2) treated patients, P-value =0.831 and both of them were statistically significant higher PASI reduction than patients with Group C,34.1±28.8, P-value =<0.001.Regarding the percentage of patients who achieved good response, there was no statistically significant difference between Group Aand Group B, 95.3% versus 70% (P-value=0.083) and both of them achieved a statistically significant higher percentage of patients with good response than Group C,47.6%, P-value=<0.001. Although the percentage of patients with complete clearance (PASI≥90%) in the Group Awas much less, 9.5%, than that of Group B, 65% (statistically significant, P-value=< 0.001), the total relapse rate during 8 weeks follow up was much lower among Group Apatients, 25% versus 70%, P-value=0.043.On the other hand no complete clearance was achieved in the Group Cand their relapse rate was 80%.

Regarding side effects: Group A, 9.5% of patients developed hypopigmentation, Group B, 10% of patients developed pyoderma and Group C, no side effects were reported. There was no statistically significant difference among the three groups regarding the frequency of side effects (P = 0.355).

CONCLUSION:

Podophyllin 5% ointment on every other day regimen was as effective as clobetasole 0.05% ointment twice daily at the end of 8 weeks treatment with no side effects and with a much lower relapse rate.

KEYWORDS: podophyllin, mild plaque psoriasis.

*Chairman of Scientific Council of Dermatology and Venereology-Iraqi Board for Medical Specializations.

**Department of Dermatology and Venereology, College of Medicine, University of Baghdad.

***Department of Dermatology and Venereology; Baghdad Teaching Hospital; Medical City.

INTRODUCTION:

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role [(1)] with an estimated prevalence ranging between 2-3% of the world's population. [(2)]

Despite major advances in the treatment of

severe psoriasis, such as the development of biological therapies, the treatment of patients with milder disease has not changed significantly over the past 10 years.[3]

The most frequently used topical treatments for mild to moderate psoriasis are topical corticosteroids, vitamin D analogues and tar. [4 - 6] Podophyllin is a well-known resin plant derivative that contains many active ingredients mainly podophyllotoxin. It has been used for treatment of genital warts for many decades.

Most recently podophyllin 25%was used successfully in the treatment of leishmaniasis[7] and curing of basal cell carcinoma. [8, 9]There is a need for the development of novel non-steroidal topical treatments for psoriasis.

So, the objectives of the current study were to evaluate the safety and efficacy of topical podophyllin 5% in ointment formulation in comparison with Vaseline and clobetasol propionate 0.05% ointment and Vaseline for the treatment of mild- plaque type psoriasis.

PATIENTS AND METHODS:

Study design

This interventional, single-blind, comparative, placebo-controlled, pilot study was carried out at the Department of Dermatology and Venereology, Baghdad Teaching Hospital, from January 2011 to July 2011.

The nature and target of this study were explained for each patient. Formal consent was taken for each patient before starting the operation, after full explanation about the nature of the disease, course, the procedure of treatment, follow up, prognosis and the need for pre and post treatment photographs. Also, the ethical approval was given by the scientific committee of the Scientific Council of Dermatology &Venereology-Iraqi Board for Medical Specializations.

The diagnosis was established on clinical basis, and the patients were not taken any topical nor systemic psoriasis treatment for at least 3months prior to starting the treatment. History was taken regarding: gender, age, occupation, residence, age of onset, duration of disease, seasonal variation, and presence of itching, history of previous treatments, medical history and family history. Physical examination was carried out to assess the features and severity of psoriasis. A total of **70** patients with mild plaque-type psoriasis were evaluated but **only 62** patients completed the study (both the treatment and follow up period). They were divided into three groups according to their treatments model:-

Group A: Twenty one patients treated with podophyllin 5% ointment every other day. Podophyllin 5%ointment was prepared by mixing 5 g of podophyllin resin powder, purchased from Merck Company, Germany, with up to 100 grams Vaseline. Patients were instructed to apply podophyllin preparation on the psoriatic plaque, avoiding the surrounding normal skin, with the use of disposable nylon gloves and to wash off the area with water and soap after 6 hours. The preparation was applied every other day for a maximum of 8 weeks.

Group B: Twenty patients treated with clobetasole propionate 0.05% ointment [manufactured by the State Company for Drug Industries and Medical Appliances Nineveh-Iraq (NDI) under licence of SDI Co.**]** twice daily.

Group C: Twenty one patients treated with Vaseline only twice daily**.**

Patients were assessed at 5 visits during the treatment period: At week zero, week 2, week 4, week6 and week 8. After the cessation of treatment, all patients were followed up every 4 weeks for 8 weeks during which relapse and any local or systemic side effects were recorded.

All patients were fully screened to record podophyllin side effects through and after treatment by clinical assessment and by doing the following investigations: General urine examination, complete blood picture, erythrocyte sedimentation rate, liver and renal function tests, serum electrolytes, fasting blood sugar, and serum amylase and serum lactate dehydrogenase. Pre, during and post treatment photographs were taken using Sony-digital, high sensitivity ISO 1600, 10.1 mega pixels, DSC-N2 optical steady shot camera, in the same place with fixed illumination and distance.

Study population

Inclusion criteria: Mild plaque- type psoriasis which is defined as PASI score of less than 10.

Exclusion criteria: pregnant or lactating women, patients younger than 18 years, , those with hepatic, renal, haematological or other systemic disorders, immunosuppression, diabetes mellitus, peripheral neuropathy, poor peripheral circulation, patients with lesions on the following sites: Scalp, face, acral parts, hands and feet, intertriginous and anogenital areas, and the following types :Pustular , and guttate were also excluded.

Efficacy evaluations

The severity, extent of psoriasis and its response

to treatment were determined according to PASI Score. Assessment of drug efficacy was based on the reduction of PASI score. Patients were considered as good responders if the reduction in PASI score was 50% or more [١٠], partial responders if the reduction in PASI score was 25-49% and poor responders if the reduction in PASI score was <25%.[١١]

Complete clearance was considered when there was a reduction in PASI score of ≥90%.Relapseis defined as loss of 50% of PASI improvement from baseline in patients who achieved at least 50% reduction in PASI score. [١٢]

Statistical Analysis

SPSS v.18 (statistical package for social sciences version 18) used for data input and analysis. Continuous variables presented as mean ± SD (standard deviation) and discrete variables presented as numbers and percentages. Chi square test for independence is used to test the significance of association between discrete variables. For testing the significance in different of means between more than two samples; ANOVA test & Kruskal Wallis test are used as appropriate for independent samples and Friedman test used for related samples.

For testing the significance of difference in means between two samples; Wilcox on rank test used to test the significance of difference in means between two related samples or in any place where the normality of distribution in question. Turkey HD test used to test the significance of difference between means of two independent samples as a complementary test after t- test looking for the exact significance of difference between two means. For testing the significance of observed difference in means of two normally distributed continuous variables; t test for two independent samples was used. Findings with P value less than 0.05 were considered significant.

RESULTS:

A total of 62patients with mild plaque-type psoriasis but patients completed the study (both the treatment and follow up period).). They were 44(70.9%) males and 18(29.0%) females, with: male: female ratio 2.3:1. Their ages ranged from 18-65years with a mean of 37.5±12.9. The newly diagnosed cases were 20(32.2%).Their disease duration ranged from 0.2-51years with a mean of 7.9±9.8, their age at onset ranged from 4-61years with a mean of29.5±13.2years. Itching was positive in 42(67.7%). The family history was positive in 20(32.5%).Their baseline PASI score ranged from 1.2-9 with a mean of 5.2±2.4.

There was no statistically significant difference in the demographic features among the three groups except for itching (P-value=0.030).

1. Group A: They were 15(71.4%) males and 6(28.6%) females with a male to female ratio of 2.4:1, their ages ranged from 18-65 years with a mean of37.6±13.6years. The newly diagnosed cases were 6(28.5%).

Their disease duration ranged from 0.2-51years with a mean of7.7±6.4. Their ages at onset ranged from 4-61 years with a mean of29.8±14.5 years. Itching was positive in 18(85.7%). The family history was positive in 5(23.8%).Their baseline PASI score ranged from1.2-9 with a mean of5.1±2.8and was reduced to 1.8± 1.7 after 8 weeks of treatment, this reduction in PASI score was statistically highly significant with P-value= <0.001.Their mean PASI reduction was 66.3±20.7 at the end of 8 weeks treatment.

2-Group B: They were 14 (70.0%) males and 6(30%) females with a male to female ratio of 2.3:1, their ages ranged from 19-61 years with a mean of37.4±10.6 years. The newly diagnosed cases were 7(35%). Their disease duration ranged from 0.3-51 years with a mean of8.1±12.2 years, their ages at onset ranged from 10-50 years with a mean of29.3±12.3 years. Itching was positive in 14(70%). The family history was positive in 8(40%).Their baseline PASI score ranged from 1.4-8.5with a meanof5.1±2.2andwasreduced to 1.8±2.2 after 8 weeks of treatment, this reduction in PASI score was statistically highly significant with P-value= <0.001.Their mean PASI reduction was 68.1±34.2at the end of 8 weeks treatment.

3-Group C: They were 15 (71.4%) males and 6(28.6%) females with a male to female ratio of 2.4:1, their ages ranged from 18-60 years with a mean of37.5±14.8years. The newly diagnosed cases were 7(33.3%). Their disease duration ranged from 0.2-42 years with a mean of7.9±10.6 years. Their ages at onset ranged from 12-60 years with a mean of29.5±13.2years. Itching was positive in 10(47.6%). The family history was positive in 7(33.3%). Their baseline PASI score ranged from 1.2-9with a meanof5.2±2.6 and was reduced to 4.6±3.3 after 8 weeks of treatment, this reduction in PASI score was statistically significant with P-value= <0.001.Their mean PASI reduction was 34.1±28.8at the end of 8 weeks treatment.

In each group the patients were subdivided into 3

groups according to their response to treatments as follow(Table-1):Group A, patients who achieved a good response were 20 (95.3%), patients who achieved partial response 25-49% were 0 (0%)and patients who achieved poor response were 1(4.7%).Group B, patients who achieved a good response were 14 (70%),patients who achieved partial response were 4 (20%)and patients who achieved poor response were 2(10%).Group C, patients who achieved a good response were 10 (47.6%), patients who achieved partial response were 9(42.8%)and patients who achieved poor response were 2(9.6%).

Topical podophyllin 5% ointment achieved a good response (≥50% PASI reduction) in about 95.3% of cases at 8 weeks of treatment but the onset of action seemed to be slow as the patients started to notice improvement after 6 weeks of treatment. On the other hand, topical treatment with clobetasol propionate ointment 0.05% induced good response in about **70%**of cases. The improvement becomes clinically evident at 4 weeks of treatment.

Hence, regarding the percentage of patients who achieved good response(≥50% PASI reduction)there was no statistically significant difference between podophyllin 5% and clobetasole 0.05%ointment treated groups, 95.3% versus 70% (P-value=0.083),table2,and both of them achieved a statistically significantly higher percentage of patients with good response than Vaseline,47.6%, P value =<0.001,tables-1and 2.The percentage of patients with complete clearance (PASI≥90%) in the group treated with podophyllin 5% ointment was much less(9.5%) than that of patients treated with clobetasole 0.05% ointment(65%) and was statistically significant, P-value=< 0.001(table-1), while no complete clearance was recorded in Vaseline treated group.

Table 1: Response to total course of treatment according to type of treatment.

Treatment Category		Response to Treatment				
		Poor	Partial	Good		
		<25%	25-49%	50-74%	75-89%	≥90% Clearance
Group A	N	1	0	10	8	2
	%	4.8	.0	47.6	38.1	9.5
Group B	N	2	4	1	0	13
	%	10.0	20.0	5.0	0.0	65.0
Group C	N	2	9	8	2	0
	%	9.5	42.9	38.1	9.5	0.0
P value = <0.001						

Table 2: Degree of response in different groups.

Response	Group A		Group B		Group C		P-value
	No.	%	No.	%	No.	%	
Good	20	95.3%	14	70%	10	47.6%	< **0.001**
Partial	0	0%	4	20%	9	42.8%	< **0.001**
Poor	1	4.7%	2	10%	2	9.6%	0.641
Total	21	100%	20	100%	21	100%	

Good response cases with PASI score reduction ≥ 50%.

Partial response cases with PASI score reduction 25-49%.

Poor response cases with PASI score reduction < 25%.

Overall P value for association is 0.011 (sig. association bet. Rx & resp.)

The percentages of PASI reduction (mean±SD) at different weeks of treatment for different groups (Table 3) were as follow: Group A, the mean reduction in PASI score was 22.7±8.6, 44.4±17.4, 56.3±20.2 and 66.3±20.7 after 2, 4, 6 and 8 weeks of treatment respectively. Group B, the mean reduction in PASI score was 46.2±32.5, 63.6±28.4, 68.3±30 and 68.1±34.2 after 2, 4, 6 and 8 weeks of treatment respectively. Group C, the mean reduction in PASI score was 27.1±17, 36±14.3, 28.0±18.4 and 34.1±28.8 after 2, 4, 6 and 8 weeks of treatment respectively.

At the end of 8 weeks of therapythe difference in

the degree of improvement (reduction in the PASI score) between podophyllin 5%(66.3±20.7) and clobetasol propionate ointment 0.05%(68.1±34.2) groups were statistically not significant with P-value = 0.831, while when the speed of recovery was compared with each other the study showed that clobetasole 0.05% ointment was much quicker in the first 2 weeks and was a bit better at the 4th week while with no statistically significant difference at 6 and 8 weeks of therapy(Table-4).However, the difference in the degree of improvement (reduction in the PASI score) between podophyllin 5% (68.1±34.2) and Vaseline(34.1±28.8) groups after 8 weeks of treatment were statistically significant with P-value = 0.001(Table-3).

Table 3: Reduction in PASI score (mean±SD) at different weeks for different groups.

Treatment Category	Reduction in PASI score (mean±SD)				P-value
Total n=62	2weeks	4weeks	6weeks	8weeks	
Group A (n=21)	22.7±8.6	44.4±17.4	56.3±20.2	66.3±20.7	<0.001
Group B (n=20)	46.2±32.5	63.6±28.4	68.3±30	68.1±34.2	<0.001
Group C (n=21)	27.1±17	36±14.3	28±18.4	34.1±28.8	0.044
P-value	0.002	<0.001	<0.001	<0.001	

Table 4: Reduction in PASI score (mean±SD) at different weeks. Comparison between podophyllin 5%every other day and clobetasole 0.05% ointment twice daily treated groups.

Treatment Category	Reduction in PASI score (mean±SD)				P-value
	2weeks	4weeks	6weeks	8weeks	
Group A (n=21)	22.7±8.6	44.4±17.4	56.3±20.2	66.3±20.7	<0.001
Group B (n=20)	46.2±32.5	63.6±28.4	68.3±30	68.1±34.2	<0.001
P-value	0.003	0.012	0.140	0.831	

The relapse rate in patients with good response was as follow : Group A,3 (15%) patients relapsed during the first 4 weeks after cessation of treatment and 2 (10%) patients relapsed after 8 weeks of stopping treatment. The total relapse rate was found in 5(25%) of cases. Group B, 6 (40%) patients relapsed during the first 4 weeks after cessation of treatment and 3 (30%) patients relapsed after 8 weeks of stopping treatment. The total relapse rate was found in 9 (70%) of cases. Group C, 5 (50%) patients relapsed during the first 4 weeks after cessation of treatment and 3 (30%) patients relapsed after 8 weeks of stopping treatment. The total relapse rate was found in 8(80%) of cases. The difference in relapse rate between the three modalities of treatments was statistically significant with p-value=0.004,and the total relapse rate during 8 weeks follow up was much lower among podophyllin 5% ointment treated patients, 25% versus 70%, and was statistically significant, P-value=0.043.

Regarding side effects: Group A,2(9.5%) patients developed hypopigmentation, Group B,2(10%) patients developed pyoderma and Group C,no side effects were reported. There was no statistically significant difference among the three groups regarding the frequency of side effects (P = 0.355).

DISCUSSION:

Despite the importance of systemic therapies and the advances represented by biologics, topical treatment will probably remain the mainstay of psoriasis therapy for most patients. [1٢]Till now unfortunately, there is no unique curative systemic or topical treatment. Although there are major advances in the treatment of severe psoriasis, such as the development of biological therapies, the treatment of patients with milder disease has not changed significantly over the past 10 years. [3]

Podophyllin is an alcoholic plant extract obtained from dried rhizomes of common plants

called emodi (*Indian podophyllum*) or *podophyllum peltatum* (May apple or Mandrake).[14]This plant derived resin contains several cytotoxic compounds in unpredictable ratio, [15]at least 16 active physiological compounds, including podophyllotoxin, picropodophyllin, α and β pellatins, podophyllotoxone and 6-methoxy podophyllotoxin, kampherol and quercetin. [14]Of thesepodophyllotoxin is the major active constituent that is a lipid soluble compound that easily crosses cell membrane. [16]

In the early nineteenth; the roots (rhizomes) had been used medicinally as a cathartic by American Indians and since the 1940s, it had been used topically for treatment of various skin lesions, especially for warts, and as an antineoplastic agent [17] but in the last century it had only been used in the treatment of anogenital warts. Most recently podophyllin had been used successfully and effectively in the treatment of cutaneous leishmaniasis [7] and basal cell carcinoma. [8, 9]

As podophyllin has multiple modes of action including: antimitotic(arrests cellular mitosis in metaphase),arresting cell differentiation, inhibiting axonal transport, protein, RNA, and DNA synthesis, inhibiting mitochondrial activity and reducing cytochrome oxidase activity and being keratolytic agent[18-20],so matching the pathogenesis of psoriasis and the mechanism of action of podophyllin, we thought wisely that this drug might possibly be effective in the treatment of psoriasis, accordingly the present work has been arranged to find a new novel therapy for psoriasis especially the mild type.

Clobetasole 0.05% ointment is a well-known effective topical treatment in psoriasis with rapid and high clearance rate but with a lot of local and systemic side effects as infection, telangiectasia, atrophy and Cushing syndrome and has a high relapse rate. In the present work when clobetasole 0.05% ointment compared with podophyllin 5% ointment we found that podophyllin was as effective as clobetasole and lacking the side effects of steroidswith a much lower relapse rate.At the end of 8 weeks of therapy we found no statistically significant difference in PASI reduction (mean±SD) between podophyllin 5% ointment (66.3±20.7) and clobetasole 0.05% ointment (68.1±34.2) treated patients, P value = 0.831.Regarding the percentage of patients who achieved good response, there was no statistically significant difference between podophyllin 5% and clobetasole 0.05%ointment treated groups, 95.3% versus 70% (P-value=0.083).The total relapse rate during 8 weeks follow up was much lower among podophyllin 5% ointment treated patients, 25% versus 70%, P-value=0.043.So we strongly recommend podophyllin as a treatment for psoriasis especially the mild plaque type.

The present work was based on a treatment regimen of twice daily 0.05% clobetasole ointment but if it's used every other day like 5% podophyllin ointment regimen, we expect that podophyllin might be much superior to clobetasole.

The present work to the best of our knowledge is the first study in this field. Further studies are highly recommended to use podophyllin in the treatment of patients with psoriasis of different ages, different severities to record any side effects. The later recommended work will be arranged soon in the near future.

Although podophyllin consists of many active ingredients but the most effective one was found to be podophyllotoxin which is much less toxic than the others so our next program is also to test the effectiveness of podophyllotoxin in treatment of psoriasis .

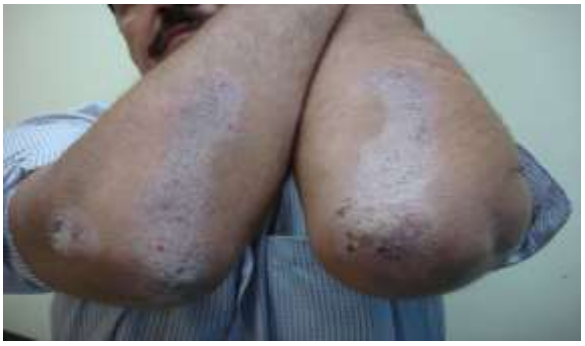

Figure 1: Fifty two years old patient with mild plaque type psoriasis Before treatment with 5% podophyllin ointment.

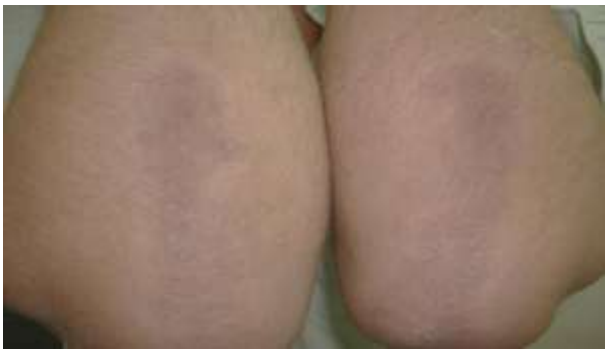

Figure 2: The same patient after 6 weeks of therapy.

CONCLUSION:

Podophyllin treatment of mild psoriasis with every other day regimen was found to be as effective as clobetasole twice daily treatment with no local or systemic side effects and the relapse rate was much lower than what had been recorded in patients using clobetasole.

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