Treatment of Perniosis with Oral Nifedipine in Comparison with Topical 5% Minoxidil Solution in Iraqi Patients. Single Blind Comparative Study

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Abstract

***Background*:** Perniosis (chilblains) is a common dermatological problem. The condition results from abnormal reaction to cold, it is seen during the cold months of winter. Many treatment modalities have been tried with variable results.

***Objective*:** To evaluate the effectiveness and safety of nifidipine in comparison with topical 5% minoxidil solution.

Methods: This was a single blind comparative therapeutic trial conducted in the Department of Dermatology and Venerology, Ramadi Teaching Hospital, Anbar, Iraq between December 2008 and March 2009. Sixty-two patients with perniosis were enrolled in this study, they were divided randomly into 2 groups, depending on the type of treatment. Group A: 42 patients received an oral sustained release preparation of nifedipine 20 mg once daily for one week then twice a day for another week. Group B: 20 patients received topical 5 % minoxidil solution applied twice daily for two weeks. Detailed history and full clinical examination were carried out for each case, regarding all relevant points related to the disease.

***Results*:** The ages ranged from 9-68 years with a mean±SD of 21±10.2 years. They comprised 37 females and 25 males, with a female to male ratio of 1.5:1. All patients did not receive any medical remedies before the start of the study. In group A: 35 patients completed the 2 weeks treatment course. Twenty (57%) patients showed good improvement and 9(26%) showed very good improvement and complete cure after 2 weeks, which was statistically significant $p<0.05$. In group B: 17 patients completed the regime. Six (35%) patients showed good improvement and 1(6%) patient showed very good improvement, when signs and symptoms disappeared after 2 weeks.

***Conclusion*:** Oral nifedipine was shown to be an effective and safe drug for treatment of perniosis, and can be used in smaller dosage, and it is superior to topical 5 % minoxidil solution. The last one showed early rapid action.

***Keywords*:** Perniosis, Iraqi patients, nifidipine, topical 5 % minoxidil
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Introduction

Perniosis (chilblains) is a common dermatological problem. The condition results from abnormal reaction to cold.[1] Thus, it is seen during the cold months of winter.[2, 3] In people with poor peripheral circulation, even moderate exposure to cold may trigger the onset of perniosis.[4, 5] It occurs chiefly on the feet, hands, ears, and face, especially in children.[6, 7] Patients are usually unaware of the injury at first, but later burning, itching, and redness call their attention.[5] Typically, there is severe localized cold erythema and swelling, but in severe cases, blistering and ulceration may develop.[5] Also there are erythematous papules and nodules, on blanching, commonly these lesions has a purpuric element, in few cases, the rash is similar to erythma multiforme.[8]

Perniosis occurs chiefly in women, with female to male ratio of 2.75:1, and their ages ranged between 2-60 years with mean age of 20.6 years.[8, 9] The duration of disease ranged from 14-21 days with mean of 17 days; sometimes the condition shows familial tendency.[2, 9] The main histological features include, dermal papillary edema, and marked perivascular lymphoid infiltrate.[9, 10, 11]

The treatment depends mainly on the protection of the affected parts against further exposure to cold. Many treatment modalities have been tried with variable results. These include rewarming of the affected parts of the body, vasodilator calcium channel blockers like nifidipine, prazosine, topical minoxidil, topical antipruritic and iontophoresis.[5, 12, 13] Also pentoxyfylline was shown to be an effective and safe drug for treatment of periniosis.[5, 14]

Nifedipine is peripheral vasodilator agent that increases blood flow to the skin in the acral parts, it has been established in the treatment of chilblains or perniosis in the dosage of 20 mg of sustained release preparation, three times a day over a six weeks period, both for treatment and for prophylaxis.[5, 15, 16] Smaller dosage of 20 mg of nifidipine, twice daily also shows good response.[13]

Minoxidil is a vasodilator selective for arterioles rather than for veins, similar to diazoxide, it is an ATP dependent K^+ chanal opener.[17] Topical 5% minoxidil solution is widely used in the treatment of scalp alopecia through its anti-inflammatory and vasodilator effects and had previously tried to be used in the treatment of perinoisis.[12, 17]

The aim of the present study is to evaluate the effectiveness and safety of nifidipine in comparison with topical 5% minoxidil solution.

Methods

This is an open comparative therapeutic trial. A total of 62 patients with perniosis were seen between December 2008 and March 2009 in the Department of Dermatology and Venerology, Ramadi Teaching Hospital, Anbar, Iraq. Detailed history was taken from each patient regarding age, sex, duration of attack, phone no, residence, history of previous attack, family history, smoking, medical history and previous treatment modalities. All patients did not receive any medical remedies before the start of the study.

Full clinical examination was carried out to assess the distribution and extent of the lesions, blood pressure before and during each visit, body mass index, any other associated skin and systemic diseases. Degree of severity was graded to mild, moderate and severe depending on a new simple grading system (table-1).

Pregnant patients and those with cardiovascular disease were excluded from the study, Also patients with known connective tissue diseases such as systemic sclerosis, systemic lupus erythematosus and those with Raynaud's phenomenon were excluded from this study. In addition to that, patients on systemic medications such as

antiplatlets, aspirin, antiepileptic and immunosuppressive therapy were also excluded. We obtained a formal consent after a full explanation of the nature of the disease.

Patients were divided randomly into 2 groups, depending on the type of treatment. Group A: 42 patients who received an oral sustained release preparation of nifedipine 20 mg once daily for one week then twice a day for another week. Sustained release preparation of nifedipine used in this study was manufactured by Egyptian int. pharmaceutical industries co. E. I.P.I.CO. Egypt. Group B: 20 patients were received topical 5 % minoxidil solution. The solution applied twice daily for two weeks. It was manufactured by ARAK pharma for pharmaceuticals Aleppo-Syria.

Patients were asked to protect themselves from further exposure to cold or fire source. The patients who showed very good or good response after completion of the 2 weeks were seen after another 2 weeks for follow up.

Regarding response to treatment, the patients were clinically evaluated after 3 days, one week and two weeks to record any side effects and to assess the clinical response to treatment which graded into very good, good, satisfactory, minimal and no response (table-2).[13]

Regarding statistical analysis, data were analyzed on computerized program: Statistical Package for Social Science (SPSS version 11), chi square was used to compare between the two groups of treatment. The probability value of less than 0.05 was considered significant.

Table-1 Shows the degree of severity of perniosis.

	Erythema	**Edema**	+\- **Vesicles**	+\- **Purpura**	+\- **Ulcers**
Mild	+	+	-		-
Moderate	++	++	**Few**	**Few**	-
Severe	+++	+++	**Many**	**Many**	**Few**

Table-2 Shows grading the response to treatment

Very good	Complete regression of erythema, edema, vesicles &ulcer
Good	Complete regression of erythema & partial regression of edema
Satisfactory	Relief in pruritus, partial regression of erythema, no regression of edema
Minimal	No relief in erythema\edema, relief in pruritus only
No response	No response

Results

A total of 62 patients were assessed and treated. Their ages ranged from 9-68 years with a mean±SD of 21±10.2 years. They comprised 37 females and 25 males, with a female to male ratio of 1.5:1. Disease duration ranged between 3-35 days with a mean±SD of 17±10.4 days. Mild grade of severity was seen in 19(31%) patients, moderate in 36(58%) patients and severe in 7(11%) patients. The location of lesions were shown in (table-3).

Regarding blood pressure, 58 patients (93%) were normotensive and 4 patients (7%) were hypotensive.

Body mass index (BMI) value was within normal in 17 patients (27%), and low BMI was recorded in 45 patients (73%).

Response to treatment as follow:

Group A: 35 patients completed the treatment course. On the third day, 12(34%) patients achieved satisfactory response and 20(57%) patients showed minimal response.

On the one week, the response was 6(17%), 16(46%) and 11(31%) patients showed very good, good and satisfactory response respectively.

On the two weeks 9(26%), 20(57%) and 5(14%) patients showed very good, good and satisfactory response respectively.

This was statistically significant with group B $p<0.05$ (Table-4).

Patients who responded to therapy were asked to stop therapy and keep on regular protective measures and followed up for another 2 weeks for clinical assessment and no recurrence was detected during follow up.

Group B: 17 patients completed the 2 weeks treatment course, On the third day, 15(88%) patients achieved satisfactory response and 20(57%) patients showed minimal response.

On the one week, the response was 6(35%) patients achieved good response and 11(65%) patients showed satisfactory response.

On the two weeks 1(6%), 6(35%) and 10(59%) patients showed very good, good and satisfactory response respectively (Table-4). Patients showed no recurrence after another 2 weeks of follow up.

Thirty one patients (70%) with moderate grade of perniosis completed the treatment courses (Group A: 23 patients, Group B: 8 patients), and the response to treatment is shown in (table-5).

No side effects were recorded in group B. While in group A: 19patients (54%) had flushing, 3(9%) had constipation and 2(6%) patients had headache, all patients tolerated the drug well. All the normotensive patients were maintaining controlled blood pressure during the course of treatment.

Table-3 shows the location of lesions in patients with perniosis n=62		
Site of lesions	**No. of patients**	**(%)**
Toes	48	77
Fingers	37	59
Both toes and fingers	23	37
Heels	12	19
Ears	5	8
Lower legs	1	1.6

Table-4 Shows the response to treatment n=52									
	3rd day			1st week			2nd week		
	A	**B**	***p* value**	**A**	**B**	***p* value**	**A**	**B**	***p* value**
Very good	--	--		6(17%)	--		9(26%)	1(6%)	<0.01
Good	--	--		16(46%)	6(35%)	>0.05	20(57%)	6(35%)	<0.05
Satisfactory	12(34%)	15(88%)	<0.01	11(31%)	11(65%)	<0.01	5(14%)	10(59%)	<0.01
Minimal	20(57%)	2(12%)	<0.01	--	--		--	--	
No response	3(9%)	--		2(6%)	--		1(3%)	--	

Table-5 Shows the response to treatment in patients with moderate grade. n=31									
	3rd day			1st week			2nd week		
	A	**B**	***p* value**	**A**	**B**	***p* value**	**A**	**B**	***p* value**
Very good	--	--		3(13%)	--		3(14%)	1(13%)	>0.05
Good	--	--		12(52%)	3(38%)	>0.05	18(78%)	3(38%)	<0.01
Satisfactory	8(35%)	6(75%)	<0.001	6(26%)	5(63%)	<0.01	1(4%)	4(50%)	<0.01
Minimal	13(37%)	2(25%)	>0.05	--	--		--	--	
No response	2(6%)	--		2(9%)	--		1(4%)	--	

Discussion

Perniosis is a common dermatological problem, the condition results from abnormal reaction to cold, with persistent cold induced constriction of cutaneous arterioles.[1, 5, 15] There are many drugs used for treatment of perniosis, but remain unsatisfactory.[5]

Nifedipine, a calcium channel blocker is a peripheral vasodilator agent, that increases blood flow to the skin in the acral parts, which has been used in the treatment in many skin vascular diseases.[5, 15, 16]

In the present study, nifedipine was shown to be effective and safe drug in the treatment of perniosis of variable severity. Response rate after 2 weeks was 57% that have good improvement and 26% have very good improvement, in which there was symptomatic relief and resolution of the lesions. The mechanism of action may be attributed to its vasodilator effect on constricted arterioles.[5, 15, 16].

Thus increasing the blood flow and tissue oxygenation, since perniosis is the result of abnormal vascular response to cold and tissue ischemia.[5]

Patients used nifedipine tolerated the side effects like flushing, constipation and headache, till the end of 2 weeks. The hypotention was not reported in those patients during treatment.

The results that were achieved with oral nifedipine were comparable to those achieved in previous studies.[13, 16] Also they were comparable to those achieved with oral pentoxyfylline.[14]

In this report, nifedipine was used in a lower dosage than the 60 mg of sustained release preparation of the drug as used in previous studies.[5, 15, 16] This may be related to the low body mass index in 73% of patients.

Minoxidil was known as systemic vasodilators[17], and topical 5% minoxidil solution were widely used in the treatment of scalp alopecia through its anti-inflammatory and vasodilator effects and had previously tried to be used in the treatment of perinoisis.[12, 17] In this study, this agent had been shown to be an effective vasodilator agent in the treatment of perniosis. After 2 weeks of treatment 35% showed good improvement and 6% showed very good improvement, without any side effects even when given in hypotenve patients. The action is probably attributed to its local vasodilator effect.

At about the 3 days of treatment, topical 5% minoxidil shows rapid effect, and 88% shows relief in pruritus and partial regression of erythema. This may be due to local direct vasodilator effect. While the action of nifedipine was slower and only 34% showed satisfaction, this was probably related to smaller dosage at the first week of treatment.

Because of the short outbreak of chilblain in Iraq, which occurs during cold months (December to March). There are small number of patients and short duration of follow up period.

In conclusion, oral nifedipine is shown to be an effective and safe drug for treatment of perniosis, and can be used in smaller dosage, and it is superior to topical 5 % minoxidil solution. The last one shows early rapid action.

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