A random comparative therapeutic trial of oral nifedipine v/s topical 5% minoxidil gel in patients of perniosis at a tertiary care center of North-western India

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Abstract

Introduction: Perniosis (chilblain) is a highly common, prolonged cold induced skin disorder, a very common nuisance in general skin OPD of northern parts of India where winters are long and prolonged and temperatures dip to almost zero. Various treatment modalities have been tried for its treatment, on time and again but none of the treatments have given optimum fast results. We conducted a study on perniosis in peak winters at one of the tertiary care center of the western India.

Aim and Objectives: To study and compare, the efficacy of oral nifedipine v/s topical 5% minoxidil Gel in perniosis.

Method: The patients clinically fitting in to the diagnosis of perniosis were divided randomly in to two groups. Necessary clinical examination and investigations were carried out to find out any other associated ailment including pregnancy. Group A was given oral nifedipine 10 mg three times daily and Group B was given topical minoxidil 5% Gel applied twice daily, topically. Irrespective of the group, all the patients were given oral antihistaminics. Both clinical and subjective responses were noted on day 3, 7 and 14, respectively.

Results: Out of 84 patients, 30 were males and 54 were females with male to female ratio of 1:1.8. The House wives were affected more among all female patients (51%). In group A and B, 42 cases were included in the study and they completed the follow up till 14th day. In group A, after second week of follow up, 25 cases noted good response, 10 cases explained it as very good and in 6 cases, satisfying response was seen which was statistically significant ($p<0.05$). In group B also, 42 cases which completed the study, after second week, 22 cases achieved satisfaction, 17 cases good and 3 cases very good response.

Conclusion: Oral Nifedipine 10 mg three times a day was more effective in lower doses among Indian patients with least possible side effects as compared to Topical 5% Minoxidil Gel therapy in the management of perniosis.

Keywords: Perniosis, Nifedipine, Minoxidil, North western India.

Introduction

Perniosis [Chilblains] are common during winter season especially in northern part of India.[1] Abnormal vascular sensitivity to cold above freezing point in a person, leads to the development of chilblains. Chilblains involves bilateral symmetrical peripheral body parts usually, although affects all ages, all races, but commonly seen in women, children, elderly and lean body mass persons.[2-4] Chilblain can be idiopathic or secondary to other systemic disorders like cutaneous lupus erythematosus, Raynauds disease, cryoglobulinemia and some leukemias.[5] Chilbalins manifest as erythematous or purplish discolouration of fingers, toes, ears and nose, accompanied by pruritus, in severe cases blistering & even ulceration can occur.[6] Diagnosis of chillblains is usually done on the basis of the clinical features only. A wide variety of therapeutic options are available in the literature but shows absence of most effective method. The treatment consists of avoiding chronic exposure to cold temperatures and treatment with agents that increase peripheral micro circulation. The calcium channel blocker, nifedipine (10 mg three times daily or 20 mg twice daily) is very effective both in increasing the rate of resolution of perniosis lesions and in preventing their reappearance.[7-9] Topical 5% minoxidil, an ATP sensitive K^+ channel opener, have anti-inflammatory and potent vasodilator effects and had been previously used in the treatment of perniosis.[10,11] Our aim was to study the efficacy of oral nifedipine in comparison to topical minoxidil among chilblain patients.

Method

A random comparative therapeutic trial was conducted in the Department of Dermatology, Government medical college, Kota from December 2013 to February 2014. The patients with symptoms of chill blains and clinically diagnosed as chilblains were included in the study. The pregnant females and those who has already taken or started treatment, were excluded from the study. From each patient, detailed history was taken regarding age, sex, duration of attack, phone no, residence, history of previous attacks, family history, smoking, medical history and previous treatment modalities. All patients did not receive any medical remedies before they were included in the study. Informed consent was taken from all the patients who were willing to participate in the study. The patients with symptoms of chill blains were segregated into two groups randomly. A thorough clinical examination was done in all patients to assess the distribution and extent of the lesions, blood pressure monitoring was done before and during each visit, body mass index (BMI) assesment was carried out and any other associated skin and systemic diseases were ruled out. Degree of severity was graded to mild, moderate

and severe depending on a new simple grading system (Table 1). Group A patients were given oral nifedipine 10 mg TDS for 14 days. Group B patients were given topical 5% minoxidil gel to apply twice daily to the affected parts. All the patients were given oral antihistaminics, Irrespective of their study group. The patients of group A were advised to report in case of any adverse reactions like flushing, headache or dizziness. The patient follow up was recorded on third, seventh and at the fourteenth day. Treatment response from the patients was noted as no response, minimal response, good, satisfactory and very good (Table 2). The statistical analysis of data was done using Statistical Package for Social Science (SPSS version-18) software. Chi-square Test was used to compare between the two study groups. The probability value of less than 0.05 was considered significant.

Table 1: Shows the degree of severity of perniosis

	Erythema	Edema	Vesicle	Purpura	Ulcer
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
Satisfactory	Complete regression of erythema & partial regression of edema
Good	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

The study was conducted in our outpatient department on total 84 patients who were clinically diagnosed as chilblains. Out of total 84, males were 30 and females were 54 (M: F-1:1.8). Age distribution ranges between 9 years to 62 years with mean 32 ± 17 years. Maximum incidence was seen in the age group 40-50 years with 21% of total. 51% of females were house wives. The incidence among rural and urban was almost same. History of having similar illness among family members was seen in half of the patients (n=44, 52%). History of recurrent episodes was seen in half of the cases (n=43, 51%). 9 cases (10%) had features resembling Raynaud's phenomenon. Toes only were affected in 40 (47%), fingers only in 3 (3.5%), plantar aspect in 10 (11.9%) and both toe and fingers in 29 (34.5%) cases respectively (Table 3). The BMI of cases were low in 58 (69%), normal in 22 (26%) and pre obese in 4 (4.7%). None of the cases was hypertensive. On examination, erythema was seen in all cases, edema was seen in 77 [Fig. 1], purpura in 20 [Fig. 2], vesicles in 11 and ulcer in 14 cases [Fig. 3] (Table 4). The severity of chilblains among both groups were as follows. (Table 5)

In group A i.e oral nifedipine, the severity of chilblains was moderate in 27, mild in 7 and severe in 7 cases. The response to the treatment was noted as no response, minimal, satisfactory, good and very good response on 3rd, 7th and 14th days (Table 6). In group A, 42 cases completed the study. After 3rd day follow up 7 cases reported response as satisfactory, 21 cases had mild and 13 cases had minimal response. On 7th day, 21 cases reported response as satisfactory, 13 cases had good, 2 cases had very good and 5 cases had minimal response. On 14th day follow up, 25 cases noted good response, 10 cases had very good and 6 cases had satisfying response.

In group B also, 42 cases completed the study. After 3 rd day, 27 cases reported good, 12 cases had satisfactory, 2 cases had very good and 1 case had no response. On 7th day, 19 cases reported satisfying, 11 cases had minimal and 9 cases had good response. On 14th day, 22 cases reported satisfactory, 17 cases had good and 3 cases had very good response.

None of our cases experienced any side effects of the drugs. The cases of chill blain with ulcers were continued with the adjunctive treatment after 14 days.

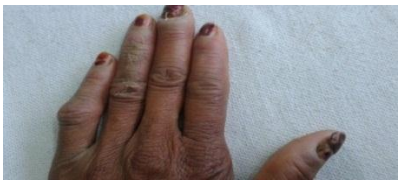

Fig. 1: Erythema and edema developing over all the fingers

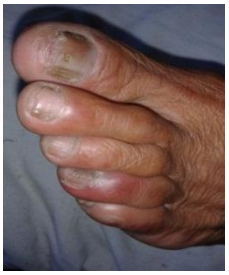

Fig. 2: resolving purpura over almost all dorsal aspects of toes

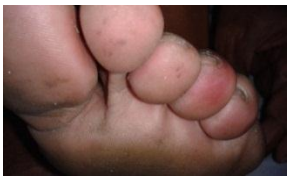

Fig. 3: erythematous patches over plantar aspect of foot

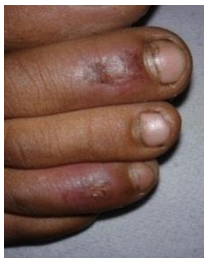

Fig. 4: ulcers developed over dorsal aspect of toes

Table 3: shows site of involvement of chilblain

Site of involvement	Total number of cases
Toes only	40
Fingers only	3
Both involvement	29
Plantar aspect only	10

Table 4: shows clinical presentation of all cases

Clinical features		Total Number of cases
Pruritus		52
Erythema	Grade 1	17
	Grade 2	52
	Grade 3	15
Edema	Grade 1	20
	Grade 2	48
	Grade 3	9
Purpura		20
Vesicle		14
Ulcer		11

Table 5: shows severity of chilblains

Severity	Group A (Nifedipine)	Group B (Minoxidil)
Mild	7	10
Moderate	27	29
Severe	7	3

Table 6: shows Response to the treatment

	On 3rd day		On 7th day		On 14th day	
	Group A	Group B	Group A	Group B	Group A	Group B
Very good	0	2 (4.7%)	2 (4.7%)	1 (2.3%)	10 (23.8%)	3 (7%)
Good	0	9 (21.4%)	13 (30%)	9 (21%)	25 (59.5%)	17 (40.47%)
Satisfactory	7 (16%)	10 (23.80%)	22 (50%)	21 (45.2%)	7(14.2)	22 (52.4%)
Minimal	21(50%)	18 (42.8%)	5	11 (26.1%)	0	0
No response	14 (30%)	3 (2.3%)	0	0	0	0
P value	1.33611		0.331058		0.001465	

Discussion

Chilblains are abnormal sensitivity of vascular response to cold temperature and high humidity, affecting acral parts of the body. They manifest as pruritic and usually tender, erythematous, inflammatory lesions and sometimes may blister due to intense itching or may even ulcerate. Several factors have been implicated in the pathophysiology. The genetic factors, hormones and increased cutaneous nerve bundles but a persistent cold induced constriction of the large cutaneous arterioles and persistent dilatation of the smaller, more superficial vessels is always present.[7] A skin biopsy may be helpful in cases where the diagnosis is in doubt. The four characteristic histopathological findings are: scattered necrosis of individual keratinocytes, marked subepidermal edema, perivascular amd peri eccrine lymphocytic infiltrate and lymphocytic vasculitis.[12]

The females were more predisposed to chilblains as seen in our study with ratio of 1.87:1. Most of the cases were from lower economic status, might be due to cold and dampy environment. The house wives who were in frequent contact of cold water due to house hold work had more chances of developing chilblains as reflected in our study also. The family members were also affected in half of the cases because environmental and housing conditions are also implicated in the development of chilblains. It may be idiopathic in majority of the cases or secondary to other systemic disorders. In our study, only 9 cases were having raynauds phenomenon. The acral parts are the typical sites involved in chilblains, toes were affected in majority cases (47%) than soles [Fig. 4], dorsum of fingers and rarely ears, tip of nose and cheeks in

decreasing order. Majority of the cases were below normal BMI (69%) and it is one of the main risk factors. The treatment of chillblains consist of avoidance of triggering factors and have many therapeutic options but none of them have been standardised.

Nifedipine, which basically is a calcium channel blocker, is a peripheral vasodilator agent. It increases blood circulation of the skin in the acral parts. It has already been used in the treatment of many peripheral vascular diseases.[7- 9, 13]

Our results show that nifedipine was effective and safe drug in the treatment of perniosis of variable severity. It although doesnot show immediate response and only minimal response in 50% of the cases till 3rd day but after one week, 30% of the cases achieved good and 50% achieved satisfactory response. After 2 weeks, 59.5% reported good and 23% had very good improvement and also, they had symptomatic relief and resolution of the lesions which was in accordance with the previous studies and also stastitically significant ($p=0.0014$).[7,8,14] The mechanism of action may be attributed to its vasodilator effect on constricted arterioles.

Minoxidil is an ATP sensitive K^+ channel reopener acting as both systemic and cutaneous vasodilator and having some anti-inflammatory action also. As a topical agent, it is used in several dermatoses attributed to its vasodilatory action. In our study, 64% patients reported good and 28 % had satisfactory improvement on 3rd day itself. Rapid action of minoxidil may be due to release of cutaneous vasoconstriction of arterioles as reported in previous study.[14] After one week, only 21% had good while 45% had satisfactory improvement. After two weeks, 52% reported satisfactory and 40% reported good response. The response noted to minoxidil was similar to the previous study.[14]

In conclusion, both oral Nifedipine and topical 5% minoxidil gel were found useful in the treatment of Perniosis. Oral nifedipine, even in low doses [10 mg TDS], was more effective in our patients in long term compared to topical 5% minoxidil gel therapy. The rapid clinical response was achieved with topical 5% minoxidil gel which suggests that it may be included in the earlier phase of the management of perniosis which is a multifactorial disease and treatment of which still needs standardisation.

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