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Original Article

Comparison of efficacy and safety of topical glyceryl trinitrate vs. oral nifedipine in idiopathic perniosis: results of a randomized clinical trial

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Abstract

Objective To compare the therapeutic efficacy and safety of topical vasodilator glyceryl trinitrate (GTN) 0.4% cream, with systemic nifedipine (10-40mg/day) in patients with idiopathic perniosis (IP).

Methods Patients with IP (n=65) were randomized into group A receiving GTN 0.4% cream (n=31) or group B receiving oral nifedipine, 10-40mg/day (n=34). They were evaluated for improvement in signs and symptoms and any side effects, every 15 days for six weeks. Primary outcome was efficacy and secondary outcome was side effects.

Results 53 patients completed the study protocol. Twenty-three out of 26 (88%) patients in group A whereas 21 out of 27 (77%) in group B had complete clearance of lesions in six weeks (p=0.52). Clearance of lesions was achieved earlier (10.9 ±6 days) in group B as compared to (16.6±11.5 days) group A (p=0.05).

Conclusion GTN 0.4% cream is an effective and safe alternative to oral nifedipine in the treatment of IP. Oral nifedipine leads to clearance of lesions earlier than GTN cream.

Key words
Perniosis, chilblains, nifedipine, glyceryl trinitrate.

Introduction

Perniosis, also called chilblains is an abnormal reaction to cold that presents in susceptible individuals.[1] Etiological factors in idiopathic perniosis (IP) include genetic predisposition, female gender and low body mass index.[2,3] In perniosis there is a persistent vasoconstriction of deep cutaneous arterioles with vasodilation of smaller superficial vessels.[4] The result is development of erythmatous macules, papules, nodules, cyanosis and sometimes ulceration associated with itching, numbness, burning or tingling and pain, usually affecting the acral areas.[1,5,6] Histopathological changes are nonspecific and include papillary dermal edema with a predominantly mononuclear perivascular and perieccrine infiltrate.[7,8] IP is generally self-limiting in 2-3 weeks but in some patients, perniotic lesions persist throughout winters. General advice about rewarming and symptomatic treatment generally suffice.[9]

Despite being a self-limiting response, IP is associated with considerable discomfort for the patients, interrupting their daily life activities. Vasodilators are the mainstay of treatment for

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such patients in addition to advice about prevention from further cold exposure. Oral nifedipine has been proved to be effective in relieving symptoms of perniosis in a double-blind, placebo-controlled trial and in an open study.[10] However, the potential side effects of oral nifedipine particularly those affecting cardiovascular system call for a cautious use.

GTN is a nitric oxide donor that produces endothelial independent vasodilatation and has been shown to increase digital blood flow in patients with primary Raynaud's phenomenon and limited cutaneous systemic sclerosis.[11] Literature is deficient regarding any trial comparing systemic vasodilators with topical ones for the treatment of IP. We therefore undertook this study to compare the therapeutic efficacy and side effects of topical GTN (0.4%) with systemic nifedipine (10-40mg/day) in patients with IP.

This study will help in providing an evidence base for the prescription of a vasodilator drug with better efficacy and fewer side effects in perniosis.

Methods

It was a parallel group, single-blind, randomized clinical pilot trial. The study was conducted after approval from institutional ethical review committee and due consideration of Helsinki declaration. It was conducted at Madina Teaching hospital, a university-affiliated teaching hospital and DHQ hospital affiliated with Punjab Medical College, Faisalabad. Faisalabad is a city in Pakistan located in the flat plains of northeast Punjab province, with an elevation of 200 metres above sea level. The temperature during winter months of December to February ranges from 4-21°C with an average rainfall of 16.4mm (0.65 inches).[12]

All patients (n=113) with IP attending Dermatology departments at two tertiary care referral centers during winter of 2012-13 i.e. from December 2012 to March 2013 were screened. Complete blood counts, ANA and RA factor were carried out to rule out systemic causes of perniosis. All eligible patients (n=65) according to inclusion and exclusion criteria were recruited. Inclusion criteria included: patients with IP defined as inflammatory lesions (erythema, cyanosis, macules, papules, nodules or ulcers) involving an acral area (hands, feet or face) associated with itching, pain or tingling sensations along with history of exposure to cold (the diagnosis was made clinically by a consultant dermatologist), both male and female patients and patients who gave written informed consent to participate in the trial.

Exclusion criteria were: patients with any systemic disease, history of Raynaud's phenomenon, taking any topical or systemic medication, pregnant or lactating females, patients under 12 years or above 60 years of age, blood pressure below 110/70 mmHg and patients with positive ANA or RA factor. Exit criteria included: failure to comply with treatment or follow-up visits, development of conditions meeting any of the exclusion criteria and patient's desire to leave the study.

After written informed consent, they were examined by a consultant dermatologist and details of disease extent and severity were recorded.

Computerized random number sequence was generated with an allocation ratio of 1:1 to allocate patients into group A (topical GTN 0.4% cream) or group B (oral nifedipine) by an independent researcher not involved in evaluation of outcomes. Sequentially numbered sealed envelopes were used to conceal allocation

and a staff nurse assigned patients to the two groups using these envelopes. Similar advice about protection from cold was given to both groups in a written form by a doctor, who was trained to follow the same sequence of instructions for those who could not read the written instructions. The patients were blinded to the type of treatment they were receiving. Patients in group A were instructed to gently massage a thin layer of GTN cream to the affected area twice a day. Patients in group B were started with nifedipine 10-20 mg/day and after one week the dose was increased to 20-40mg/day taken as nifedipine retard tablet, if they did not experience any side effects like light-headedness, dizziness or flushing.

They were evaluated for improvement in signs and symptoms and any side effects, every 15 days by the same consultant, for six weeks. Complete resolution of signs and symptoms was taken as the end point. Primary outcome was efficacy and secondary outcome was side effects.

Data were analyzed using SPSS version 17. The therapeutic effects of two treatments were compared using t-test and chi-square test. *P* value <0.05 (confidence interval of 95%) was taken as significant.

Results

One hundred and thirteen patients presenting with IP were screened. Thirty-one were excluded based on exclusion criteria (**Figure 1**). Seventeen patients declined to participate in the study. Sixty-five enrolled patients were randomized into group A (n=31) and group B (n=34). Twelve patients, 5 from group A and 7 from group B were exited from the study as they failed to comply with follow-up visits. Nine patients had to discontinue treatment (3 from group A and 6 from group B) due to side effects (n=3), worsening of disease (n=2) and treatment perceived as ineffective (n=4). Twenty-three patients in group A and 21 in group B had complete resolution of lesions. Data analysis was based on complete data of 53 patients.

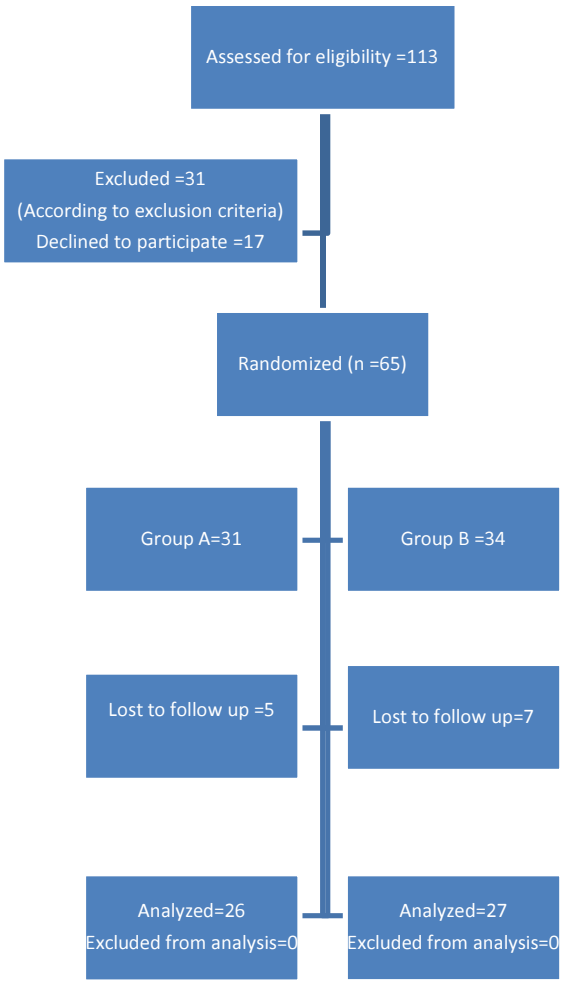

Figure 1 Patient flow diagram.

Demographic profile and disease parameters of patients in the two groups are compared at

Table 1 Demographic profile and disease parameters of study population at baseline.

Demographic variable	*Group A N=31*	*Group B N=34*	*P value*
Mean age (years)	20.3 ±5.7	21.5±8.38	0.386 *
Gender Female/Male	24/7	29/5	0.414 **
BMI	20± 3.5	21±3.8	0.764*
Rural/urban	5/26	8/26	0.456**
Disease parameters			
Episode first/recurrent	3/28	8/26	0.127**
Severity			0.542**
Mild	4	2	
Moderate	17	18	
Severe	10	14	
Area of involvement			0.553**
Feet	17	16	
Hands and feet	14	17	
Hands, feet and face	0	1	

P value calculated by t-test * and chi-square test**

Table 2 Comparison in terms of outcome and side effects between two groups.

Outcome	*Group A N=31*	*Group B N=34*	*P value*
Lost to follow-up	5	7	0.52**
Discontinued treatment	3	6	
Treated successfully	23	21	0.52**
Mean time for clearance of lesions (days)	16.6 ± 11.5	10.9 ± 6.0	0.05*
Feet, mean (range)	16 (3-45)	10.66 (3-25)	
Hands and feet, mean (range)	16.9 (4-30)	11.45 (5-20)	
Side effects	1	5	0.110**

P value calculated by t-test * and chi-square test**

baseline in **Table 1**, indicating no significant difference (*P*> 0.05) between the groups.

Twenty-three out of 26 patients (88%) in group A whereas 21 out of 27 (77%) in group B had complete clearance of lesions (*P*=0.52). However, clearance of lesions was achieved earlier 10.9 ± 6 days in group B as compared to 16.6±11.5 days in group A (*P*=0.05). Five patients in group B experienced side effects particularly severe headache to the extent that they had to discontinue nifedipine and were shifted to GTN cream, whereas only one patient in group A had mild local irritation after use of GTN cream (*p*=0.110), **Table 2**.

Discussion

Many studies published in the recent past indicate that IP is not an uncommon presentation in South East Asian countries during winters.[13-16] It is considered to be more common in young females, usually with a low BMI.[17,18] This was also reflected in our study with 81.5% of the patients being females. Mean age of female patients was 21.49 ± 7.5 years. However the mean BMI for female patients was 20.461. Fourteen patients (26%) were underweight (BMI<18.5), 30 (62%) were normal (BMI 18.5-24.9), 4 (7.5%) were overweight (BMI 25-30) and one patient was obese (BMI>30). All were nonsmokers.

This randomized controlled study showed that clinical outcome in patients with IP using oral

nifedipine is not significantly different from those using GTN cream (0.4%) in terms of complete clearance of lesions. However, with systemic nifedipine the response is quicker. This can be explained on the basis of mode of delivery of the drug. Multiple factors such as the amount of GTN cream applied, frequency of hand washing and wet work may have affected the results of group A.

In the double-blind, placebo-controlled trial by Dowd *et al.*[19] establishing nifedipine as the drug of choice for perniosis in 1986, 10 patients receiving nifedipine had complete clearance of lesions within 7-10 days, whereas in our study the mean duration of clearance of lesions with nifedipine is 10.9 days with a range of 4-16 days even with a much lower dose i.e. 20-40mg/day as compared to 60mg/day in study by Dowd *et al.*[19] In the open study by Rustin *et al.*[10] the duration of clearance of lesions was much longer; mean 21 days for lesions on hands and feet and 23 days for lesions on feet alone. The reason was that only 17 of the 31 patients could tolerate a dose up to 40 mg/day of nifedipine.[10]

In another trial comparing nifedipine with diltiazem by Patra *et al.*[20], 21 patients showed 80-90% improvement in signs and symptoms of perniosis with 30-40mg of nifedipine in Indian population. Only one patient in this study developed dizziness with nifedipine at this dose. However, in our study 5 patients developed headache that was severe enough for them to discontinue the treatment. One reason may be that most of the patients in study by Patra *et al.*[20] were adult males (M: F=18:7) including soldiers whereas in our study majority of the patients were young females (M:F=29:5) with a mean BMI of 21±3.8 in group receiving nifedipine. In group A, only one patient developed mild local irritation with GTN cream that settled within a few hours without any treatment.

In study by Anderson *et al.*[11] on patients with primary Raynaud`s phenomenon and limited cutaneous sclerosis, GTN cream proved to increase digital blood flow when measured by laser Doppler imaging.[11] The same mechanism that produces increased digital blood flow in Raynaud's phenomenon and systemic sclerosis i.e. nitric oxide-induced vasodilatation seems to be effective in patients with idiopathic perniosis, as well.

GTN topical preparation in combination with calcium channel blockers is advocated in Raynaud's phenomenon, particularly in cases not responding to calcium channel blockers alone.[21] However, no clinical trial with topical GTN has been conducted on patients with IP so far. Occasional mention of GTN cream as a treatment of IP can be found.[22] Pilot studies with nitroglycerine ointment for prevention of cold injuries have been conducted on soldiers and workers residing at high altitude with good results in India.[16,23] The results of our study clearly indicate a place for GTN cream in the treatment options for IP.

Conclusion

Topical GTN 0.4% cream is an effective and safe alternative to oral nifedipine in the treatment of idiopathic perniosis. Systemic nifedipine leads to clearance of lesions earlier than topical GTN cream.

Disclosure of conflict of interest None declared.

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