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General Medicine

CHILBLAINS (PERNIOSIS): EXPERIENCE IN FIELD, TREATMENT STRATEGIES: A FIELD STUDY

KEY WORDS: Chilblains, Clopidogrel, Foot parade, Nifedipine, Pentoxifylline

Lt Col (Dr) Rajendra Pal Singh*	Assistant Director Health, Ministry of Defence, Govt of India *Corresponding Author
Lt Col (Dr) Dheeraj Kumar	Internal Medicine Specialist – Base hospital lucknow
Lt Col (Dr) Binu Sekhar M	Aviation Medicine Specialist
Lt Col(Dr) Sanjay Kumar Sharma	Gynaecologist- Army hospital Research & Referral.
Lt Col (Dr)Dronacharya Routh	Associate prof, Department of surgery AFMC Pune
Col (Dr) BS Deswal	Prof & Head, Dept of Community Medicine, SGT Medical College, Gurugram

ABSTRACT

Introduction: Chilblains are common among helicopter aircrew and maintenance personnel operating at high altitude locations. As the recommended behavioural preventive measures were inadequate, a study was undertaken to see the effectiveness of available pharmacological measures.

Methodology: 42 healthy males with chilblains participated. 6 subjects, who were doing recommended behaviour measures only, were taken as controls. Rest 36 subjects were equally divided into four groups with four different pharmacological regimens which were foot parade + Clopidogrel (treatment-I), foot parade + Clopidogrel + Pentoxifylline (treatment-II), foot parade + Clopidogrel + Nifedipine (treatment-III) and foot parade + Clopidogrel + Pentoxifylline + Nifedipine (treatment-IV).

Results: Of the total 42 patients, 32(76.2%) were recovered and 10(23.8%) were not recovered during the study observation period of 10 days. Control and treatment-I groups had shown recovery rate of 16.7% and 44.4% respectively. Rest had 100% recovery. When treatment duration for clinical cure was analysed among different groups, the mean±SD in days for control, treatment I, II, III and IV were 9.0±0.0, 9.3±1.1, 4.4±0.5, 4.4±0.7 and 3.2±0.6 days respectively. The control and treatment-I groups took significantly longer time for recovery than other three treatment groups (p<0.001). Treatment groups II and III were not found to have any significant difference (p=1.0) between themselves, while treatment group-IV had shown further advantage (p=0.047). The mean±SD of pre-treatment and treatment duration in days were 3.8±1.5 and 5.9±2.7, respectively. They did not have any significant correlation (r=-0.05, p=0.78).

Conclusion: Pharmacological strategies have shown added advantage both in cure rate and rapidity of recovery.

INTRODUCTION

Extensive use of air support has been provided in very high altitude areas at Himalayas and Siachen glacier mainly with the help of helicopters.¹ These include landing sorties at several high altitude helipads as well as supply dropping sorties at various camps located at different parts of the glacier.¹ Most of those areas are snow bound throughout the year with minimum temperature of -50°C in winters and -15°C in summers.¹ The altitude of operations ranges from bases located above 10000 ft to locations close to 20000 ft.² The aircrew and support personnel deployed at such locations are at risk of suffering from cold related injuries throughout the year. The effects of severe cold climates are more often felt by maintenance personnel than the aircrew.³ They regularly come in contact with cold metal parts of the aircraft or different kinds of oils and lubricants while doing maintenance works.³ Even though the multilayered protective winter clothing issued to the armed forces personnel are very much effective, there are several reported cases of cold related injuries.⁴ Moreover decrease in the manual task performance, especially for skilled performance requiring finger tactility and manual dexterity, while wearing multilayered winter clothing may encourage some maintenance personnel to use minimum clothing or temporarily remove the existing clothing and thus predisposing to cold injuries.² Susceptible personnel are easily affected. Exposure to cold climatic conditions can lead to variety of maladies which occur mainly because of inability of human body to completely adapt to

cold environments.^{5,6} Chilblains (a.k.a Perniosis) is a severely disturbing form of localised cold injury which commonly occurs after exposure to non-freezing temperatures and increased humidity.^{6,8} It presents as an inflammatory, erythematous or violaceous, pruritic or painful lesions that most commonly appear on the distal extremities, with affinity for the dorsal aspects of the digits.^{5,9}

Even though the exact pathophysiology is still unclear, this is widely believed to occur due to an abnormal vascular response to cold conditions.^{5,10} The condition is believed to have a genetic predisposition.¹¹ Heterozygous mutations in TREX1 gene was reported to cause familial chilblains.¹² The histological nature of the disease includes dermal oedema and a lymphocytic perivascular as well as perieccrine infiltrate.^{8,13,14} The exact incidence and prevalence in various geographical regions are not available, however historically up to 50% of women developed chilblains in wartime conditions in northern Europe.⁹ In England, the annual incidence is stated as 10%.⁷ In India, the populace located at northern as well as north-eastern states are particularly vulnerable during winter months. However, the exact incidence is unknown.

Majority of cases of Chilblains are idiopathic¹⁰, while rest may be secondarily associated with systemic diseases like chronic myelocytic leukemia,¹⁵ cold agglutinins, cryoglobulinemia,^{8,16} cryofibrinogenemia, macroglobulinemia, dysproteinemia,

anorexia nervosa^{14,16} and systemic lupus erythematosus.^{8,14,15} Most of the literature reveals that idiopathic chilblains subsides itself with adequate protective clothing and warm living conditions, it may take weeks to get complete cure.^{6,10,15} Cure may be delayed in case of continued or recurrent exposures to the cold climate.^{5,7} Besides spontaneous recovery, several treatment modalities have been advocated in literature. Ultraviolet phototherapy has been tried as a prophylactic measure without much benefit.^{5,7} Treatment with calcium channel blocker nifedipine^{7, 15, 17}, topical steroid creams^{15, 18}, prazocin¹⁴, oral vitamin D3¹⁹, topical antipruritics¹¹ and nicotinic acid¹⁸ etc had shown mixed results. However, considering the existing knowledge on pathophysiology of chilblains, the common medications used in peripheral vascular disease patients such as antiplatelet drugs like aspirin²⁰ or clopidogrel²⁰, methyl xanthine derivatives like pentoxifylline^{14,20} and long acting vasodilators like nifedipine retard^{7,15,17,18} or amlodipine⁷ may be beneficial. However, sufficient data of their use and comparison of effects of different medications on chilblains is lacking especially for patients who continued to stay in potential climatic conditions. Recommended management consists of reassurance, keeping the part dry and warm, immersion in warm water followed by thorough drying and application of Vaseline (petroleum jelly) or cold cream.^{21,22} However such measures are found not to be effective once the clinical features of chilblains are underway. Considering the necessity of early recovery and minimal disruption for flying fitness it is imperative to consider more aggressive treatment of chilblains.

To understand the advantage of introducing pharmacological treatment in chilblains, a study was designed among the affected population at a high altitude aviation base of Indian Army located at 10,300 feet altitude.

MATERIAL AND METHOD

This study was designed as a non randomised trial study. Subjects were selected from patients reported at an Army medical facility in high altitude area. Clinically diagnosed cases of chilblains as per presentation^{11,14} were selected. Cases of any underlying systemic disease or ongoing medication were excluded. Convenience sampling was adapted as the numbers of cases were limited. Informed written consent was obtained from each subject who volunteered to participate in this study.

The age, date of onset of symptoms/ signs, date of commencement of treatment, duration of commencement of disease to the initiation of treatment, symptoms and signs and distribution of disease, treatment outcome and the number of days of treatment to get complete clinical improvement were recorded. Few subjects (n=6) who continued to do only behavioural measures such as keeping the limbs dry, wearing multiple woollen socks, winter boots, gloves, washing regularly with warm water and applying cold cream were selected as controls. Such behavioural measures are generally called as foot parade. Rest of the patients (n=36) were randomly divided into four groups to be offered different modes of pharmacological treatments apart from the aforementioned behavioural measures. The drugs and the dosage selected were tab Aspirin 325 mg OD²⁰, tab Nifedipine retard 20 mg BD^{7,21,23} and tab Pentoxifylline 400 mg TDS²⁰. However, the first two patients who were prescribed tab Aspirin reported next day with gastritis. Hence tab Aspirin 325 mg was replaced with tab Clopidogrel 75 mg²⁰ with same dosage frequency, and those two cases were not included in the study. Thus the final treatment groups were foot parade + Clopidogrel group (treatment I), foot parade + Clopidogrel + Pentoxifylline group (treatment II), foot parade + Clopidogrel + Nifedipine group (treatment III) and foot parade + Clopidogrel + Pentoxifylline + Nifedipine group (treatment IV). All cases were observed for a maximum period of 10 days.²³ If any patient did not show improvement in his condition after 10 days, he was not considered part of the study group any further while his treatment was changed over to treatment IV (foot parade + Clopidogrel + Pentoxifylline + Nifedipine group).

Statistical Analysis

Data was analysed to find the added advantage of any pharmacological intervention and also to see whether the delay in starting the pharmacological treatment adversely affects the recovery. Percentage distribution of age, clinical features and recovery were computed. Age, pre-treatment duration and treatment durations were compared between different groups using one way ANOVA followed by Bonferroni post hoc analysis. Chi-square test was used to analyse proportional difference in recovery. Pearson correlation was used to analyse the relation between pre-treatment duration and treatment duration. Level of significance was taken as 5% (p<0.05).

RESULTS

Treatment and clinical data of 42 chilblains patients were collated in this study. All reported cases were male military personnel who were affected with chilblains of both feet without involvement of any other extremity.

Out of 42 subjects, 6 did only foot parade and were taken as the control group. Rest 36 subjects were divided into four treatment groups of 9 each. From the history and clinical examination findings all were presumed to be cases of Idiopathic chilblains. They are from different ranks comprising of officers, JCOs and OR. Incidentally 2 out of 42 patients were aviators. The mean \pm SD of age of various treatment groups did not show any significant difference (F=1.27, p=0.30) (Table-1). The reported symptoms were itching, redness, pain and swelling of multiple toes (Table-2) and common signs were erythema, oedema and tenderness (Table-3).

Out of total 42 cases, 32 were cured after treatment and the rest 10 did not respond to the treatment protocol instituted for this study (Table-4). After 10 days of maximum observation period, they were given treatment protocol IV and all 10 were completely cured. However, hereafter they were excluded from this study.

When the recovery benefits of different treatment groups are compared using Chi-square test, it was found that significant difference (p<0.001) was present between the groups (Table-4 & Fig-1). The Control (p=0.002) and treatment I (p=0.03) groups were having significantly less cure rate compared to other three treatment groups (Table-5). However, the difference between controls and treatment I group was not found to be significant (p=0.58).

The duration for starting treatment regimen (pre-treatment duration) was not found to be significantly (F=0.16, p=0.96) different among the groups while the duration of treatment (treatment duration) for attaining complete clinical cure was found to be different significantly (F=96.3, p<0.001) between different treatment groups (Table-2). When post hoc analysis was done, it was found that treatment groups II (p<0.001), III (p<0.001) and IV (p<0.001) are significantly better than controls and treatment I group. Treatment IV was found to be beneficial over treatment II and III (p=0.047) (Table-6).

When the pre-treatment duration was correlated with duration of treatment required for clinical cure, there was no significant correlation (r=-0.05, p=0.74) (Fig-2)

DISCUSSION

This study comparing different pharmacological modalities to treat Idiopathic chilblains was conducted in the high altitude areas (10,300 feet) of the Indian Himalayas during winter months from October 2011 to March 2012.

The study population, being military personnel, were all males although the literature mentions increased incidence in females.⁶ In this study the mean age of affected population was 30.6 \pm 5.0 years. Even though, it is reported that adolescent and younger age groups are affected more often²⁴, the study population in this study mainly included younger and middle aged adults. Although the age distribution cannot be commented upon, the treatment groups did not show significant (p=0.30) difference in their age.

During the maximum defined observation period of 10 days in this study, 76.2% of patients recovered clinically while the remaining 23.8% did not respond favourably. Out of the 10 unrecovered cases of chilblains, half belonged to the control group while the other half were in treatment I group. When the recovery rate among different treatment groups were compared, it was found that treatment II (foot parade + Clopidogrel + Pentoxifylline), treatment III (foot parade + Clopidogrel + Nifedipine) and treatment IV (foot parade + Clopidogrel + Pentoxifylline + Nifedipine) were significantly better than controls (foot parade only) ($p=0.002$) or treatment I (foot parade + Clopidogrel) ($p=0.03$). However, it was found that adding Clopidogrel alone to foot parade did not have any significant advantage ($p=0.58$). As 100% cure rate was obtained for treatment II, III and IV, any advantage among them could not be computed further. A similar study published by Patra et al., comparing the therapeutic benefits of nifedipine and diltiazem reported 100% cure rate in nifedipine group compared to 47% cure rate in diltiazem group after 21 days observation.²⁵ Rustin et al reported that the treatment with nifedipine has significantly reduced dermal oedema and perivascular infiltrate in cases of chilblains.¹⁷

The mean duration for reporting to medical centre after the onset of initial symptoms (pre-treatment duration) was 3.8 ± 1.5 days and the same did not differ significantly among different treatment groups ($F=0.16, p=0.96$) in this study. However, it was found that the treatment groups differed significantly ($F=96.3, p<0.001$) in duration of attaining clinical cure after commencement of treatment (treatment duration). Treatment II, III and IV were found to be superior to controls ($p<0.001$) and treatment I ($p<0.001$) in terms of treatment duration. Treatment IV was found better than treatment II ($p=0.047$) or III ($p=0.047$). Rustin et al reported that nifedipine significantly reduced the time of clearance of existing lesions and prevented the developments of new chilblains.¹⁷ Patra et al., also reported significantly faster relief with nifedipine as compared to diltiazem.²⁵ However, Clopidogrel alone did not improve the treatment duration as compared to controls ($p=1.0$) in this study. Treatment groups II and III also did not differ between themselves ($p=1.0$).

When the pre-treatment duration was compared with treatment duration, there was no significant correlation $r = -0.05, p=0.74$). This shows that the pre-treatment duration did not affect the duration for recovery after treatment. However, this may have occurred in this study since the mean pre-treatment duration was $3.8 (\pm 1.5)$ days where all the subjects were already doing preventive measures such as foot parade even before reporting the symptoms. This particular factor may have also influenced the treatment duration.

The medications used in this study are Clopidogrel, Pentoxifylline and Nifedipine. Clopidogrel is a thienopyridine derivative which reduces platelet aggregation by inhibiting the ADP pathway of platelets. It irreversibly block the ADP receptor on platelets. Anti thrombotic effect starts within 5 hours after initial dose. The usual dose is 75mg once daily and this achieves maximum platelet inhibition.²⁶ The FDA approved indications of clopidogrel include peripheral arterial disease.²⁷ Pentoxifylline is a methyl xanthine derivative. It can decrease blood viscosity and improve blood flow under certain conditions.²⁸ The rheologic modifying effect by increasing the deformity of red blood cells is the basis of beneficial effects of pentoxifylline.²⁹

Nifedipine is the prototype of dihydropyridine family of calcium channel blockers. The L-type calcium channel is the dominant type in cardiac and smooth muscles and is known to contain several drug receptors. Almost all type of smooth muscles especially vascular smooth muscle is dependent on trans-membrane calcium input for normal resting tone and contractile responses. These cells can be relaxed by calcium channel blockers. In the vascular system arterioles appears to be more sensitive than veins.⁴ The vascular smooth muscle relaxation effect of nifedipine occurs at significantly lower concentrations than those required for prominent direct effects on the heart.²⁹ A significant body of

evidence suggests that calcium channel blockers interfere with platelet aggregation and prevent atheroma formation in vitro.⁴ In therapeutic doses the reported adverse effects are minor in the form of flushing, dizziness, nausea, constipation and peripheral oedema.^{4,7,23}

In our study we have observed the potential benefits of drugs which are commonly recommended for peripheral arterial diseases, such as pentoxifylline, clopidogrel and nifedipine, are useful in chilblains in terms of cure rate and duration for clinical recovery. These medications are very safe in therapeutic dosages and the adverse effects are very unlikely to have any long term or permanent effects on the body.^{4,23,26,28} Hence the recommendation of these medications, as per our study, as in the treatment IV regimen was found to be highly beneficial and can be administered for personnel suffering from chilblains who are to continue their stay at cold climates. This can leads to early recovery and attaining fitness including that for flying at the earliest.

LIMITATIONS OF THE STUDY

This study has several limitations. The difficulty in planning and executing such research in the field conditions was the prime reason for the limitations. Sample size of the study was limited and when the sample was divided into different groups the size became even smaller. Hence the statistical value of the results is limited. Convenience sampling was adopted and subjects were assigned to different study groups in the order of reporting to medical facility. A stratified random sampling would have been ideal. Blinding was not being done since similar tablets of different medications and placebo was not available off the shelf. Hence both the investigator and subjects were aware of the nature of medication.

One more treatment group with combination of foot parade, pentoxifylline and nifedipine would have been beneficial to understand the effect of clopidogrel in the treatment of chilblains. All the subjects were young and middle aged army personnel. There were no females among the subjects. Hence, generalizations can only be made with caution. Also the study did not incorporate the chances of recurrence after treatment and also the requirement of chemoprophylaxis for chilblains.

CONCLUSION

Overall the study infers the importance of adding pharmacological treatment for chilblains. Such pharmacological strategies may be more important for personnel who continue to stay in potential climatic conditions. Although adding pentoxifylline or nifedipine or both to clopidogrel while continuing the behavioural measures have much better cure, this study failed to show whether early administration of pharmacological treatment has any additional recovery benefit. The small sample size and study design limitations do not allow authors to make bold recommendations, however a large study on this subject is strongly recommended.

Tables and figures

Table-1: Comparison of mean \pm SD of age, pre-treatment duration and treatment duration of different treatment groups

Treatment group	N	Age (yrs)	Pre-treatment duration (days)	Treatment duration (days)
Control	6	28.1 \pm 3.6	3.8 \pm 1.2	9.0 \pm 0.0
Treatment-I	9	30.5 \pm 6.3	3.6 \pm 1.6	9.3 \pm 1.1
Treatment-II	9	31.3 \pm 5.5	4.0 \pm 1.7	4.4 \pm 0.5
Treatment-III	9	33.3 \pm 4.5	3.8 \pm 1.7	4.4 \pm 0.7
Treatment-IV	9	29.1 \pm 4.0	4.1 \pm 1.6	3.2 \pm 0.7
Total	42	30.6 \pm 5.0	3.8 \pm 1.5	5.9 \pm 2.7
Significance using one way ANOVA	F value	1.27	0.16	96.3
	P value	0.30 ^{NS}	0.96 ^{NS}	<0.001***

NS: Not significant; *** Highly significant

Table-2: Distribution of symptoms

Sr No	Symptoms	Frequency (N)	Percentage (%)
1	Itching	10	23.8
2	Redness, pain, itching	9	21.4
3	Redness, swelling	11	26.2
4	Redness, swelling, pain	12	28.6
	Total	42	100

Table-3: Distribution of signs

Sr No	Symptom	Frequency (N)	Percentage (%)
1	Erythema	13	31
2	Oedema, erythema	21	50
3	Tenderness, oedema	8	19
	Total	42	100

Table-4: Treatment group and recovery data cross tabulation

Treatment group	Treatment mode	Recovery		Total
		Yes	No	
Control	Foot parade	1 (16.7%)	5 (83.3%)	6 (100%)
Treatment-I	Foot parade + Clopidogrel	4 (44.4%)	5 (55.6%)	9 (100%)
Treatment-II	Foot parade + Clopidogrel + Pentoxifylline	9 (100%)	0	9 (100%)
Treatment-III	Foot parade + Clopidogrel + Nifedipine	9 (100%)	0	9 (100%)
Treatment-IV	Foot parade + Clopidogrel+ Pentoxifylline + Nifedipine	9 (100%)	0	9 (100%)
Total		32 (76.2%)	10 (23.8%)	42 (100%)

Chi-square test:
Level of significance (p value): <0.001***, Degree of freedom: 4
Chi-square value: 25.16

*** Highly significant

Table-5: Significance of difference between treatment group and recovery data using Fisher's exact test

Sr No	Treatment groups compared	p value
1	Controls Vs Treatment I	0.58 ^{ns}
2	Control Vs Treatment II/ III/ IV	0.002**
3	Treatment I Vs Treatment II/ III/ IV	0.03*

NS: Not significant; ** Very significant; * Significant

Fig- 1: Distribution of patients based on recovery in different treatment groups

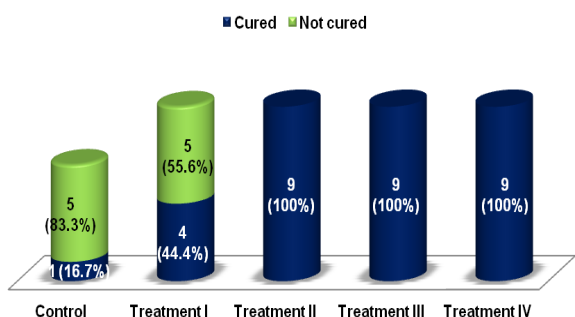
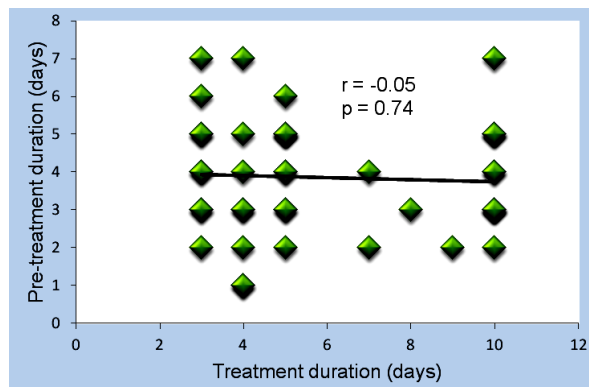


Fig-2: Pearson correlation (r) analysis between pre-treatment duration and treatment duration in days



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