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Original Article

Comparative study of testing the efficacy of topical clobetasol versus clobetasol plus glyceryl trinitrate (GTN) ointment for the symptomatic relief of chilblains

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Abstract

Objective To test the efficacy of topical Clobetasol versus Clobetasol plus Glyceryl trinitrate (GTN) ointment for the symptomatic relief of chilblains.

Methods This study was conducted over a period of two months starting from 1st December 2020 till 31st January 2021 at the outpatient of Dermatology department at Punjab Rangers Teaching Hospital, Lahore. A total number of sixty patients who presented to skin OPD with chilblains were enrolled in the study and were divided into two groups. One group was taken as cases (40) and the other as controls (20). Cases were labeled group A and controls were labeled group B, both were tested for five variables i.e. pain, pruritus, edema, erythema and ulcerations. Both groups were advised application of the topical preparation after washing & drying the affected area twice daily. Group A was prescribed application of topical GTN along with clobetasol ointment, while group B was advised to apply clobetasol only. Both the groups were advised follow up to the OPD after two weeks to compare the effectiveness of each & were assessed for the improvement in all the five tested variables which were pain, pruritis, erythema, edema and ulceration.

Results On the first follow-up after regular application of the prescribed preparation for two weeks, it was noted that out of 40(100%) patients in group A, significant improvement was seen in 32(80%) in all the tested variables, whereas among 20(100%) patients of group B, 9(45%) reported improvement in pruritus, pain, erythema and edema.

Conclusion Glyceryl trinitrate when added with clobetasol has a better and rapid relief of symptoms as compared to when used alone.

Key words
Glyceryl trinitrate (GTN), clobetasol, chilblains, Raynaud's disease.

Introduction

Chilblains also known as pernio are painful inflammation of small blood vessels in skin that occur in response to repeated exposure to cold.[1] It is a clinical presentation in which vasoconstriction of small vessels of extremities causes itching, erythema, edema and blistering on hands, feet, nose and ears.[1] Chilblains are most common in Pakistan in winters with peak incidence between December and February. There are a limited number of topical

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preparations being used for the relief of these symptoms, among which steroids are the most commonly prescribed ones. The main effect of Corticosteroids is their anti-inflammatory & vasoconstrictive properties**.** Topical GTN in ointment form has long been used for symptomatic treatment of anal fissures by lowering the sphincter pressure and healing anal fissure. Its principal pharmacologic action is relaxation of vascular smooth muscle mediated via the release of nitric oxide.[1,2] Many researches have been done on its efficacy for Raynaud's disease, applying it repeatedly on the affected areas increases warmth, diminution of pain, improvement in consistency of the tissues, shedding of gangrenous tissue and improvement of ulcers of the affected area.[1] Chilblains (also known as perniosis) is a localized disease which presents as inflammatory, erythematous, intensely pruritic or painful acral lesions. It is seen in susceptible individuals after prolonged exposure to nonfreezing cold temperatures and damp conditions. It is characterized by inflammation of the small blood vessels caused by an abnormal reaction to the cold resulting in bluish-red discoloration of the skin that can cause pain, intense itching, burning/ stinging, and swelling of the skin, especially as the body becomes warmer. One hypothesis is that cold weather causes the subcutaneous arterioles to tighten or constrict & when rewarmed, blood leaks into the tissue and causes the skin to become edematous. This edema irritates the nerves and can cause pain.[6] The erythema usually develops over the fingers, toes, lower legs, heels, ears and nose; rarely it can also appear on the thighs and buttocks. In severely affected individuals with idiopathic chilblains the lesions range from reddish-blue macules to bullae and ulcers.[7] This may result in infections or even scarring upon healing.

Lesions begin to appear approximately 12-24 hours after exposure to cold, spontaneous resolution is sometimes seen in about three weeks.[8] Lab investigations and cutaneous biopsy may be done when lesions are persistent or when there is suspicion of an underlying systemic disease. Many times chilblains is confused with Raynaud's phenomenon which is a vascular disorder with somewhat similar clinical presentation. Raynaud's however is aggravated by stress, smoking, anxiety or with any underlying connective tissue disorder. It is characterized by spasms of arterioles, especially in the fingers and toes due to cold exposure.[9] This causes an abnormal vascular response which presents as pruritic, erythematous to cyanotic lesions with symmetrical involvement of fingers, toes, nose and ears. In most of the cases the disease is limited with no systemic involvement. Some cases with thigh and buttock involvement have also been reported.[10] The diagnosis is purely based on history and clinical examination. It mostly affects young and middle-aged women and children, annual recurrences are seen with spontaneous resolution as the weather changes. Patients with chronic recurrent disease are advised for follow-up as there can be an underlying connective-tissue disease. Overall the prognosis is good.

What is the role of clobetasol in chilblains? Topical application of Corticosteroids stimulate the production of a glycoprotein called lipocortin which inhibits the activity of phospholipase A2 affecting the arachidonic acid metabolism and interleukin-1 formation thus producing anti-inflammatory effects, which results in constriction of the blood vessels, thus reducing localized swelling and pain.[12]

How glyceryl trinitrate helps in reducing the symptoms of chilblains? Glyceryl Trinitrate is a vasodilating agent. Its mechanism of action is to relax smooth muscle of the vessel walls. Glyceryl Trinitrate produces dilation of both arterial and venous beds.[13] There is not much

work being done on chilblains, since this is an extremely painful and debilitating disease, we planned to conduct a study and select a drug which could show significant response in shorter period of time to inculcate a sense of relief and satisfaction to the patients. Also GTN is easily available and is cost-effective.

Methods

This prospective, comparative study was conducted at the outpatient department of dermatology at Punjab Rangers Teaching Hospital over a period of two months starting from December 1st till the end of January. A total of 60 patients of chill blains compatible with the inclusion criteria were enrolled in the study.

Inclusion criteria Patients with chill blains belonging to any gender and age group.

Exclusion criteria Patients suffering with any co-morbidity like diabetes mellitus, hypertension, connective tissue disease, Raynaud's disease and those already on oral nitroglycerine were not included in the study.

Upon the first visit, informed consent was taken to ensure their compliance thus avoiding the bias, the demographic data including gender and age recorded, detailed history regarding the disease was taken & examination was done. The severity of disease was assessed depending upon five variables which were pain, pruritus, erythema, edema and ulcerations.

Pain was graded as mild to moderate & severe.

- *Mild to moderate:* Patient either requiring no oral analgesic, or at the most 1-2 times a week.
- *Severe:* Requiring painkiller at least four times a week.

Pruritis was similarly categorized into mild to moderate & severe.

- *Mild to moderate:* Maximum 3-4 times a day.
- *Severe:* most of the day.

Subjective variables: Patients having only edema & erythema were categorized under mild to moderate disease.

Objective variables: Patients with ulcerations were categorized under severe disease.

Gender: Of the total 60 (100%) enrolled patients, 22 (36.66%) were males and 19 (63.33%) were females **(Table 1)**.

Age: the age range of the patients was 5.5to 58. Mean age of patients was 26±5. The mean age of female patients was 15±10 and the mean age of male patients was 35±15. Among them 14 (23%) patients were between 1-10 years of age, 24 (40%) patients were between 11-20 years old, 12 (20%) patients were between 21-30 years of age, 6 (10%) patients 31-40 years and 8 (13%) patients >41 years **(Table 2)**.

Area involved: The disease was variable in distribution with the feet affected in all 60 patients. There was involvement of only toes in 45(75%) patients, both toes & digits in 15 (25%). 18 (30%) had lesions over both dorsal and plantar aspects of their toes, 27 (45%) had lesions over the dorsal aspect only. There was only 1 (1.6%) patients with involvement of the ears.

Variables: Of the total 60 (100%) patients, severe pain was reported in 21 (35%) patients, while 39 (65%) complained of only mild to moderate pain, pruritis was reported in 57 (95%) patients while the remaining 3 (5%) had no pruritus **(Table 3)**. Among these variables, 25 (63%) patients with mild to moderate disease and15 (37%) patients with severe disease were

enrolled in group A **(Figure 1)**. Patients in group B 12 (60%) had mild to moderate disease and 8 (40%) had severe disease **(Figure 2)**.

Results

All the patients given GTN ointment alonwith clobetasol categorized as group A patients are summarized in **Figure 1.** Patients prescribed clobetasol alone were categorized under group B and are shown in **Figure 2.** Total number of 60 (100%) patients were enrolled, among them 22 (37%) were males and 38(63%) were females. There was no age limit and the median (range) age was 21 years.

Skin lesions localized on feet (45 patients) and/or hands (15 patients) and presented as generalized erythematous or edematous swelling to ulcerated lesions (severe disease). Patients complained of pain, pruritus and swelling more pronounced on exposure to warmth (warm water, clothes etc.).

Group A patients were then sub-categorized under mild-moderate and severe disease. Number of patients with mild-moderate disease were 25 (63%) among which 23 (58%) showed significant improvement on their first follow-up. Total patients with severe disease were 15 (37%), 11 (27%) of whom showed remarkable response to treatment.

Group B patients were also sub-categorized in the same manner, 12 (60%) with mild-moderate disease and 8 (40%) with severe disease. On their first follow-up 9 (45%) out of 12 with mild-moderate disease showed good response to treatment, while 3 (15%) out of 8 patients with severe disease responded to treatment, however, the response was somewhat delayed and not as significant as group A patients **(Figure 3).**

Discussion

Although affecting a limited area in the body, chilblains is a very painful & debilitating condition causing gre & functional disability to its sufferers restricting their daily life functioning.[14] Although the seriousness of these handicaps varies considerably, a large number of patients still present with unexpectedly severe complaints. Not much is known about this disease and very fewer studies have been conducted regarding its treatment. Sitting in a dermatology setup, we encounter many such patients in the extreme winter season, who look up to us to seek at least some rapid relief from their pain. Topical corticosteroids have long been used for the symptomatic relief of chilblains, working to variable extent from patient to patient, causing improvement in the severity of symptoms, but the relief is very little & temporary. There still remains a need to add some alternative treatment, some vasodilator, acting at the vascular level, either locally or systemically that would aid in further relief of these symptoms. Niphedipine, categorized under the calcium channel blocking anti-hypertensive group, has been & is still under usage for this purpose owing to its vasodilator effect. Although it stays a very effective treatment, it has many side effects including headaches, dizziness, flushing etc. thus advocating its use in severe disease only. The exigency for an adequate & effective treatment for patients with moderate to mild disease is still demanded.

A study conducted in 2017 by Dr Souwer to see the effect of corticosteroids concluded that betamethasone was in no way superior than placebo for the treatment of chilblains.[15] One double-blind placebo-controlled randomised study conducted on patients with severe chilblains indicated that nifedipine with its efficient vasodilating effect when administered at a dose of 20-60mg a day decreased pain, soreness and reduced the time for clearance of lesions.[16] However its use should be limited to

severe disease only.

GTN is a vasodilator which has long been used for the symptomatic relief of anal fissures. It works by dilating the blood vessels in and around the fissures, increasing the blood supply to the affected area, leading to rapid healing. Most of the patients with acute fissures recover with GTN treatment alone.[17] A study conducted in 2015 by Verma demonstrated significant improvement in chilblains with use of topical GTN with almost complete regression in chronic cases as well. He enrolled 22 patients of which 18 had a significant improvement in first week and complete regression in the following week, 2 patients with relapse were given GTN for another week with good results, the efficacy of treatment was somewhat delayed in patients with chronic disease.[18] Another study was conducted to see the effect of GTN on patients with Raynaud's disease, the results although really good, were temporary thus proving that GTN was only for the palliative treatment.[19]

Since chilblains also share the same pathophysiology as Raynauds, vasoconstriction & the compensatory vasodilatation of peripheral arteries being the main cause of pain, erythema and cyanosis and in chronic cases, ulcerations, it was desired to carry out a study regarding the role of this vasodilator drug in relieving the symptoms of chilblains. GTN is being used at different setups. A comparative study that we conducted between GTN alongwith clobetasol showed a remarkable improvement in shorter period of time (58% improvement in mild-moderate cases and 27% improvement in severe cases) as compared to clobestasol (45% improvement in mild-moderate cases and 15% in severe cases) when advocated alone.

Clobetasol proves to have good results in reduction of the acute flares of erythema and edema but pain factor persists which hinders with the patient's compliance to treatment and weakens their confidence in therapy. The rationale for the study was to bring GTN to use for chilblains as a definitive treatment with rapid relief of signs and symptoms as it is easily available and also cost friendly. On the first follow-up after 2 weeks, majority of the patients in group A were satisfied with the results and reported their relief from symptoms within first 5-10 days of use of GTN along with clobetasol, on the other hand patients in group B although showed improvement to moderate extent but with little improvement in pain.

Chillblains from a patients perspective is very harmless disease, offering only limited therapeutic treatments. we strongly urge further research into the disease and its therapy

Conclusion

With regards to no observed side-effects, easy availability, low price and rapid action of GTN, it is a good drug to be used with clobetasol as a first-line treatment of mild- moderate and severe chilblains as compared to clobetasol alone. Due to its effectiveness and safe use in any age, this drug is a promising treatment for children under the age of 5 as well. Despite the discussions going on about the use of oral nitroglycerine for the treatment of chilblains, it should be kept in mind that it is not safe in all the age groups and it brings along with it a countless number of side effects.

Therefore we highly encourage using GTN along with clobetasol to attain rapid and promising results for chilblains.

References

1. Danzl, Daniel F. 2021. Nonfreezing Tissue Injuries. March. https://www.merckmanuals.com/professional/injuries-poisoning/cold-injury/nonfreezing-

tissue-injuries?redirectid=2106&qt=Chilblains&alt=sh#sec21-ch319-ch319b-702.
2. Mohan, Swati. 2020. From symptoms to treatment all you need to know about chilblains. January 4. https://www.business-standard.com/article/health/from-symptoms-to-treatment-all-you-need-to-know-about-chilblains-120010400969_1.html.
3. Leo Francis Tauro, corresponding author Vittal V. Shindhe, P. Sathyamoorthy Aithala, John J. S. Martis, and H. Divakar Shenoy. 2011. Comparative Study of Glyceryl Trinitrate Ointment Versus Surgical Management of Chronic Anal Fissure. *Indian J Surg*.2011;73(4):268–77.
4. P., Verma. Topical Nitroglycerine in Perniosis/Chilblains. *Skinmed*.2015;13(3): 176-7.
5. M. E. Anderson, T. L. Moore, S. Hollis, M. I. V. Jayson, T. A. King, A. L. Herrick. Digital vascular response to topical glyceryl trinitrate, as measured by laser Doppler imaging, in primary Raynaud's phenomenon and systemic sclerosis. *Rheumatology*.2002; 41(3):324-8.
6. Okafor, Amarachi. 2020. national organization of rare disorders. Accessed 2021. https://rarediseases.org/rare-diseases/perniosis/#:~:text=Perniosis%20is%20characterized%20by%20inflammation,as%20the%20body%20becomes%20warmer.
7. Michelle Pratt, Farhan Mahmood, Kirchhof. 2021. Pharmacologic Treatment of Idiopathic Chilblains (Pernio): A Systematic Review. March 2. https://journals.sagepub.com/doi/full/10.1177/1203475421995130.
8. Akkurt ZM, Ucmak D, Yildiz K, Kutlu Yürüker S, Özkaya Celik H. Chilblains in Turkey:a case-control study. An Bras Dermatol.2014;**89(1)**:44-50.
9. Newman, Tim. 2017. What you need to know about Raynaud's disease. December 19. https://www.medicalnewstoday.com/articles/176713.
10. Brannon, Heather L. 2013. Understanding How Topical Steroids Work. July 13. https://www.verywellhealth.com/how-topical-steroids-work-1068833.
11. Stewart, Michael. 2018. Glyceryl trinitrate rectal ointment (Rectogesic). October 11. https://patient.info/medicine/glyceryl-trinitrate-rectal-ointment-rectogesic.
12. Sergio Vano-Galvan, Antonio Martorell. 2012. Chilblains. *CMAJ*.2012;**184(1)**:67.
13. Michele S Maroon, William D James. 2020. Pernio. February 20. https://emedicine.medscape.com/article/1087946-overview#a2.
14. Stewart, Michael. 2018. Glyceryl trinitrate rectal ointment (Rectogesic). October 11. https://patient.info/medicine/glyceryl-trinitrate-rectal-ointment-rectogesic.
15. Souwer, Ibo H. Assessing the effectiveness of topical betamethasone to treat chronic chilblains: a randomised clinical trial in primary care. *Br J Gen Pract*.2017;**67(656)**: e187–e193.
16. Rustin MH, Newton JA, Smith NP, Dowd PM. The treatment of chilblains with nifedipine: the results of a pilot study, a double-blind placebo-controlled randomized study and a long-term open trial. *Br J Dermatol*.1989;**120(2)**:267-75.
17. Leo Francis Tauro, corresponding author Vittal V. Shindhe, P. Sathyamoorthy Aithala, John J. S. Martis, and H. Divakar Shenoy. 2011. Comparative Study of Glyceryl Trinitrate Ointment Versus Surgical Management of Chronic Anal Fissure *Indian J Surg*.2011;73(4):268–77.
18. Verma, Prashant. Topical Nitroglycerine in Perniosis/ Chilblains. *Skinmed*.2015;**13(3)**: 176-7.
19. Martin S. Kleckner, Edgar C. Allen, Khalil G. Wakim. The Effect of Local Application of Glyceryl Trinitrate on Raynaud's. *Circulation*.1951;**3**:681–689. https://www.ahajournals.org/doi/10.1161/01.CIR.3.5.681.