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Original Research Article

Cryotherapy with liquid nitrogen for chronic and recalcitrant intertrigo of toe webspaces

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ABSTRACT

Background: The inflammation of the toe web spaces is known as foot intertrigo. Most commonly caused by candida. Important predisposing factors such as diabetes mellitus, obesity and immunosuppression lead to persistence and recurrence. Cryotherapy is a promising, safe, cost-effective, easily available therapeutic approach to treat recalcitrant intertrigo compared to available topical medications. Aim of the study was to observe the clinical improvement and therapeutic response of recalcitrant intertrigo and to observe treatment response based on photographs.
Methods: A total of 30 patients who were clinically diagnosed with chronic candida intertrigo (CI) who fulfilled the inclusion and exclusion criteria were enrolled. Cryotherapy was administered with 3 cycles of freeze and thaw of 30 seconds each, every 2 weeks for a maximum of 3 treatment sessions. Follow-up of patients were done for 4 months.
Results: Among 30 patients treated, 21 patients showed excellent clinical response, 6 patients showed good response. Only 2 patients showed poor response. Minimal side effects were observed, of which transient pain at the cryotherapy site is the most common. Diabetes was the most common comorbidity with poor response to treatment and recurrence.
Conclusions: Cryotherapy can be used as a safe modality of treatment for recalcitrant CI cases unresponsive to topical therapy by providing faster therapeutic response and improving the quality of life in these patients.

Keywords: Chronic candidal intertrigo, Cryotherapy, Toe intertrigo, Recalcitrant toe intertrigo, Liquid nitrogen

INTRODUCTION

Intertrigo is a chronic inflammatory disease that occurs as a response to pressure, heat, maceration, or decreased circulation of air in the opposing skin surfaces.[1] Most commonly caused by Candida.

Candidal intertrigo (CI) mainly affects 4th and 5th web spaces of toes.[2] Symptoms like pain and itching substantially reduce the quality of life, resulting in high morbidity.

The incidence and recurrence of the disease are facilitated by a multitude of predisposing factors, especially obesity, diabetes mellitus and immunosuppressive conditions. There are various topical antifungal therapies available, but they all fail to treat the recurrence and chronicity of the disease.[2]

The use of liquid nitrogen cryotherapy in CI helps in removal of macerated hyperkeratotic tissue in web spaces by formation of intracellular ice crystals, causing changes in cellular organelles and disrupting the candida infected cells.[3,4]

So far only limited studies are done on this treatment modality which is published. Therefore, our study aims to observe the clinical improvement and therapeutic response

of recalcitrant intertrigo of toe web spaces by using cryotherapy as a safer and cost-effective modality by enhancing the quality of life.

METHODS

Study design

The design of the study was interventional and prospective study.

Sample size

Sample size was calculated using the formula= $\frac{4PQ}{d^2}$

Where P is the percentage of side effects observed and $Q = 1 - P$

Statistical method and tool used in the study

Statistical Package for Social Sciences (SPSS) for Windows version 22.0 released 2013. Armonk, NY: IBM Corp., was used to perform statistical analyses.

Data was expressed in percentages.

Assuming the percentage of adverse effects is 50% (as no similar studies are available in literature).

Sample size was calculated based on the formula=$\frac{4PQ}{d^2}$

Where P – percentage of adverse effects=50%=0.5; d – precision=20%=0.2; Q – 1-P=1-0.5=0.5

$$\frac{4 \times 0.5 \times 0.5}{0.2 \times 0.2} = \frac{1}{0.04} = 25{\sim}30\ sample\ size$$

Ethical approval

Approval was taken from the institutional ethical committee.

Participants

A total of 30 clinically diagnosed patients of chronic recalcitrant intertrigo who fulfil the inclusion and exclusion criteria were enrolled in the study. The study was conducted from August 2019 to December 2019 at the department of dermatology, venereology and leprosy at Kempegowda Institute of Medical Sciences, Bangalore.

Inclusion criteria

Chronic candidal intertrigo (≥6 months) recalcitrant to previous treatments with adequate topical and/or systemic anticandidal therapies; patients with age more than 18 years above were included in the study; and patients who have given written informed consent were included in the study.

Exclusion criteria

Patients with secondary bacterial infection; cold intolerance, arterial disorder, Raynaud's phenomenon or any other systemic diseases; patients who are not willing for follow up; and pregnant and lactating women were excluded.

Participants' demographic details and relevant history of the disease, duration of symptoms was recorded as per the pre- structured proforma.

Chronic CI was diagnosed by history, clinical examination, potassium hydroxide swab and fungal culture in each patient. Recording the demographic data in preformed questionnaire and documenting the clinical photographs at the first visit and then on further follow up was done for each patient.

Liquid nitrogen cryotherapy was administered with a hand held cryogun (Figure 1) until uniform frosting (30 seconds) (Figure 2).

A repeat freeze cycle was administered immediately after a thaw of 30 seconds. 3 cycles of the same was done in one setting.

The therapy was performed every 2 weeks for a maximum of 3 treatment sessions.

Patients were instructed to apply mupirocin ointment only over the treated areas twice a day for 7 days and were advised not to use any other topical antifungals.

All patients were examined every 2 weeks for 2 months and then monthly once for next 2 months.

At each visit, the responses were assessed with clinical examination, photographs and monitored for side effects. Most of the patients had excellent response after 3 sessions, few attained complete clearance after 2 sessions.

Figure 1: Hand held cryogun.

Figure 2: Uniform frosting 30 seconds.

The treatment response was graded as follows: excellent response – complete sloughing off the hyperkeratotic/macerated tissue; good response – significant thinning of hyperkeratotic tissue; poor response – only slight thinning of hyperkeratotic tissue; and no response – no improvement (Figures 3 and 4).

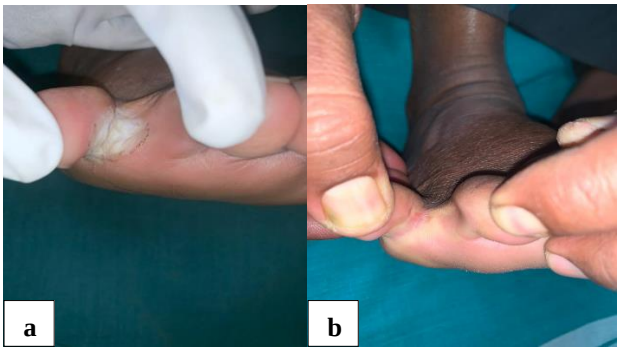

Figure 3: Excellent response after completion of 3 sessions (a) at 1st session- macerated sodden webspace and (b) after completion of 3 sessions- complete clearance.

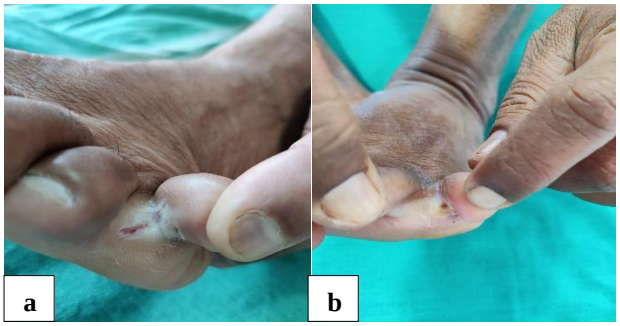

Figure 4: Poor response at end of 3 sessions (a) at 1st session –macerated 5th toe web space, and (b) poor response noted after 3 sessions.

RESULTS

A total of 30 patients were enrolled in our study. Out of 30 patients included in the study, 28 (93.3%) were male and 2 (6.7%) were female.

The duration of chronic intertrigo ranged from 8 months to 60 months with a mean of 15.67 months.

Diabetes patients had more pain, blister formation, bacterial infection and depigmentation compared to other comorbidities.

In all the 21 (70%) patients who showed excellent response of which 14 of them needed three sessions as seen in Figure 3, 5 of them needed two sessions and 2 of them needed only 1 session of cryotherapy to obtain the desired effect.

Good response was observed in 6 (20%) patients out of which 4 of them needed three sessions and 2 of them needed two sessions. Poor response was observed in 2 (6.6%) patients and 1 (3.3%) patient showed no response. Recurrence was observed in 1 patient after 6 months (Figure 4).

Treatment related adverse effects included early adverse effects (0-6 days) that is transient pain was observed in 23 (76.7%) patients which subsided on taking non-steroidal anti-inflammatory drugs (NSAID) for 2 days, blister formation was noted in 16 (53.3%) patients (Figure 5).

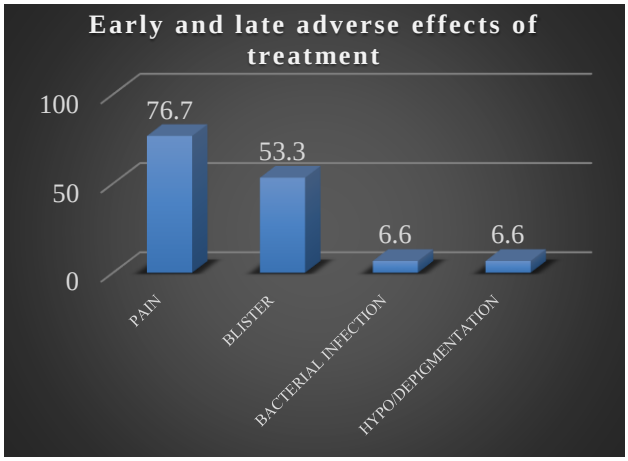

Figure 5: Treatment related side effects.

Figure 6: Depigmentation of cryotherapy site.

Figure 7: Secondary bacterial infection.

Delayed adverse effects (7-14 days) such as hypo or depigmentation was seen 2 patients (6.6%) and secondary bacterial infection was seen only in 2 (6.6%) patients, 4 patients had no adverse effects (Figures 6 and 7). Poor response and no response were seen among diabetic patients.

DISCUSSION

Cryotherapy is application of cold temperature substance such as liquid nitrogen, nitrous oxide, dry ice to a diseased tissue, in a regulated and controlled manner. Liquid nitrogen of minus 196 degree Celsius was used in our study. It is a safe, convenient, cost effective, efficacious, and cosmetically appropriate treatment option for various skin disorders.

When the cryogen is sprayed, heat is rapidly transferred from the tissue to the cryogen, resulting in ice formation in the extracellular compartment. Ice crystals can cause mechanical damage to the cell membrane. In addition, intracellular ice formation occurs, causing organelles such as mitochondria and the endoplasmic reticulum of the candida infected cells. Slow thawing exposes cells to toxic substrates for longer periods of time during recrystallization, increasing cell damage. Denaturation of fungal cell wall proteins can occur because of cryotherapy. Crust formation as a result of local ischemia following the procedure can aid in the clearance of chronic infective tissue.[3,4]

Toe web intertrigo refers to a variety of diseases of varying clinical symptoms. It may appear as a chronic erythematous desquamative eruption or an outburst of exudative, macerated, inflammatory eruption. Associated symptoms can be mild to severe, and in some cases, they can be incapacitating.[5]

Moisture trapped in deep skin folds, where air circulation and natural evaporative drying are reduced, aids intertrigo. Foot intertrigo is usually seen in people who participate in sporting, occupational, or leisure activities and is linked to closed toe or tight-fitting shoes.[6]

Dermatophytes and bacterial infections often occur together in interdigital areas. Yeasts are also commonly isolated from interdigital intertrigo.[7] Cellulitis is more likely in patients with serious toe web intertrigo who are overweight or have diabetes. Erythematous desquamating infection can be more chronic than acute, and it can cause a painful, exudative, macerating inflammation in the feet, resulting in functional impairment.[8]

Therefore, detection of infection, prevention of triggering factors, and appropriate treatment may prevent subsequent cellulitis and erysipelas of the leg and other potential complications. As a result, early detection of infection, avoidance of triggering factors, and timely treatment can help to avoid cellulitis and erysipelas of the leg, as well as other complications.[9]

Recurrent bouts of CI trigger a local hyperkeratotic response, which reduces the effectiveness of topical antifungal drugs, resulting in chronic infection and treatment. Heat, humidity, and outdoor activities should all be avoided by patients.

It is beneficial to improve air flow and natural evaporative drying of the region for people who have toe web intertrigo by placing a separator between the toes to separate the toe web interspaces. Physical activity is normally beneficial, but patients should shower afterward and keep their intertriginous areas completely dry. Toe web intertrigo can be avoided by wearing open-toed shoes.[8]

Hence our study shows successful treatment of such recalcitrant cases of chronic intertrigo by using cryotherapy. There were very minimal adverse events noted in our study and thus makes it a safer and cost-effective modality of treatment and reduces the burden of patients.

Limitations

This study has certain drawbacks, despite being a novel therapeutic intervention. The smaller sample size, subjective method of assessment of clinical response and also limited studies are done on this treatment modality therefore, lesser comparison between the other studies are the few flaws of our study.

CONCLUSION

Cryotherapy is a promising and safe treatment option for recalcitrant and persistent intertrigo that has failed to respond to topical and systemic treatment.

In comparison to other treatment alternatives, this is a cost-effective procedure.

Its day-care procedure involves fewer follow-up, with minimal side effects, which promotes patient compliance as well. As with long-term topical and oral therapies, it has a faster response and a longer remission time, enhancing

patients' quality of life and reducing financial burden. Therefore, cryotherapy can be used as a first line therapy in such recalcitrant cases.

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Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

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