

Original Research Article

Comparative evaluation of therapeutic efficacy of cryotherapy with liquid nitrogen versus oral terbinafine pulse in finger nail onychomycosis

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ABSTRACT

Background: Onychomycosis is a fungal infection of the nail unit and can be caused by dermatophytes, yeasts and non-dermatophyte moulds. None of the treatment modalities yield consistent results. Cryotherapy as a treatment modality has not been studied in its management.

Methods: 80 clinically confirmed cases of onychomycosis were enrolled for the study. Cases in group 1 were given liquid nitrogen cryotherapy with dipstick method for 12 weeks at 2 weekly intervals and cases in group 2 were given oral terbinafine in a dose of 500 mg daily for a week/month for 3 months. After 12 weeks cases in both groups were followed up at intervals of 3 weeks till 24 weeks.

Results: At week 12, 40% of the patients in group 1 achieved clinical cure which was comparable to treatment with oral terbinafine pulse which was 45% and G3 response was attained by 20% of the patients in group 1 and 17.5% patients in group 2. The results at 12 weeks were comparable in two groups and p value was insignificant. At the end of study duration, clinical cure was achieved in 32.5% in group 1 and 62.5% of patients in group 2 and p value was highly significant.

Conclusions: The results of cryotherapy were inferior to oral terbinafine pulse. Though results with cryotherapy were comparable to oral terbinafine pulse at 12 weeks, at 24 weeks oral terbinafine pulse proved to be a treatment option in finger nail onychomycosis.

Keywords: Nail, Onychomycosis, Tinea unguis, Cryotherapy, Oral terbinafine, Anti-fungal pulse therapy

INTRODUCTION

Nails are window to overall well-being, enhance manual dexterity and have cosmetic relevance. The nail is an important 'tool' and it adds subtlety and protection to the digit.¹ The term 'onychomycosis' refers to fungal infection of one or more of the components of the nail unit and can be caused by dermatophytes, yeasts or non-dermatophyte molds.² Reports concerning the prevalence of onychomycosis are conflicting with estimates ranging

from 2-3% to 13% in the western population. In India it is a common infection and accounted for 20% of all nail diseases until 1980s.³ Management of onychomycosis is often challenging and has been attempted throughout the ages, but success has been limited until the current decade. Oral terbinafine has a high clinical and mycological cure. Terbinafine is conventionally given in daily dose for 6-12 weeks. Since it persists in the nail apparatus for long durations even after the therapy is discontinued pulse therapy is a good option.⁴

To achieve adequate therapeutic response, it is pertinent to address the issues of patient compliance by reducing the duration, adverse effects as well as the cost of treatment, at the same time providing therapeutic efficacy equivalent to the widely used standard treatment modalities.

This emphasizes upon the need to evaluate the role of newer treatment options in onychomycosis. Therefore, in our study, the role of cryotherapy was evaluated as novel therapeutic modality in onychomycosis and its therapeutic efficacy was compared to oral terbinafine pulse treatment.

Aim and objectives

Aim and objectives were to evaluate the therapeutic efficacy of oral terbinafine pulse in finger nail onychomycosis; to evaluate the therapeutic efficacy of cryotherapy with liquid nitrogen in fingernail onychomycosis; comparative evaluation of oral terbinafine pulse versus cryotherapy with liquid nitrogen in fingernail onychomycosis.

METHODS

Study area

Department of Dermatology, Venereology and Leprology at Guru Gobind Singh Medical College and Hospital, Faridkot.

Study population

Eighty patients of onychomycosis (calculated using Danial sample size formula: $n = Z^2 P(1-P)/d^2$) with positive microscopic evidence, divided in 2 groups of 40 each were enrolled from outpatient department of Dermatology, Venereology and Leprology of Guru Gobind Singh Medical College and Hospital, Faridkot from June 2013 to December 2013.

Criteria for diagnosis

Diagnosis was made on the basis of clinical criteria and KOH examination for fungal hyphae.

Clinical

Primary criteria

White/yellow or orange/brown patches or streaks.

Secondary criteria

Secondary criteria were onycholysis, subungual hyperkeratosis/debris, nail plate thickening.

Laboratory

Positive microscopic evidence with KOH examination (presence of fungal hyphae/spores/yeast cells).

Inclusion criteria

Inclusion criteria were patients of both sexes between the ages twenty to sixty years and patients having onychomycosis of fingernails.

Exclusion criteria

Exclusion criteria were patients having history of cold urticaria, cryofibrinogenaemia or cold intolerance, patients having Raynaud's disease, patients having nail dystrophy secondary to psoriasis, lichen planus, contact dermatitis, or traumatic onychodystrophies, patients with deranged liver functions and patients with deranged renal functions (creatinine clearance <50 ml)

A detailed history and clinical examination were conducted in each case and recorded on a prescribed Proforma. A written informed consent was taken from each patient before starting the study.

Each patient was subjected to the following investigations at the time of reporting complete blood counts; fasting blood sugar; complete urine examination; liver function and renal function tests; venereal disease research laboratory test; human immunodeficiency virus enzyme-linked immunosorbent assay; KOH examination from subungual debris and nail clipping.

Procedure

A total of 80 patients with fingernail onychomycosis confirmed microscopically were divided in two groups of 40 each, 40 patients assigned to group 1 were treated with cryotherapy using liquid nitrogen as cryogen. Affected nails were first cleaned by povidone iodine and after drying, double freeze thaw cycles with Paint brush/dip stick technique using liquid nitrogen as cryogen were given on the affected nail plates. In the paint brush technique liquid nitrogen was applied starting at the lateral edge of the lesion and carried back and forth over the entire extent of the lesion. In the Dipstick method a cotton tipped applicator dipped in liquid nitrogen was applied firmly to the lesion until a narrow halo of white ice was formed around the bud.

After completion of the procedure, antibiotic cream was advised for local application twice a day over the lesions subjected to cryotherapy to prevent any secondary infection. 40 patients under group 2 were treated with oral terbinafine pulse therapy.

Schedule of treatment and follow up

Group 1- sessions of cryotherapy were given fortnightly with a minimum of four applications and if subungual hyperkeratosis persisted, another 2 applications were given at an interval of 2 weeks making a total of 6 applications. After 12 weeks patients were followed up regularly at the interval of three weeks for another twelve weeks.

Group 2- patients were prescribed oral terbinafine as pulse therapy with daily dose of 250 mg twice daily for 1week, followed by a gap of 3weeks and two similar pulses were given making a total of 3 pulses. After 12 weeks patients were followed up regularly at the interval of 3 weeks for another 12 weeks.

At every follow up visit, response to treatment was recorded and graded both objectively and photographically. Response was graded as follows:

G0- No response, G1-<25% improvement, G2-26% to 50% improvement, G3-51% to 75% improvement, G4>76% improvement

Study design

Comparative clinical trial.

Statistical evaluation

The results achieved were statistically analyzed with the help of chi square test and other appropriate formulae including the Man-Whitney test after follow up of 12 weeks.

RESULTS

The age of the patients ranged between 20 and 60 years. The maximum age of the patient was 60 years and the minimum age enrolled was 20 years. More than 50% of the subjects in our study belonged to the age group between 21 to 40 years.

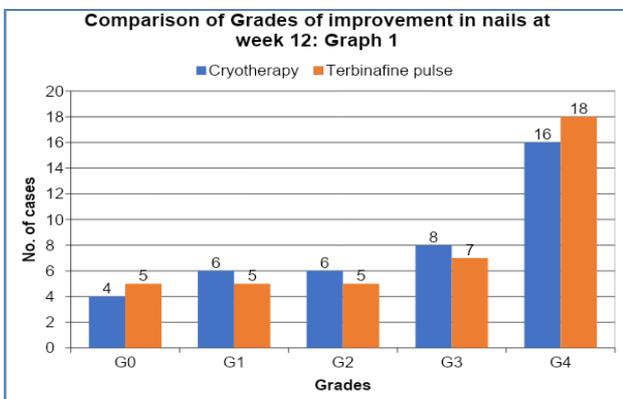


Figure 1: Comparison of grades of improvement in nails at week 12.

P value= 0.793 (insignificant)

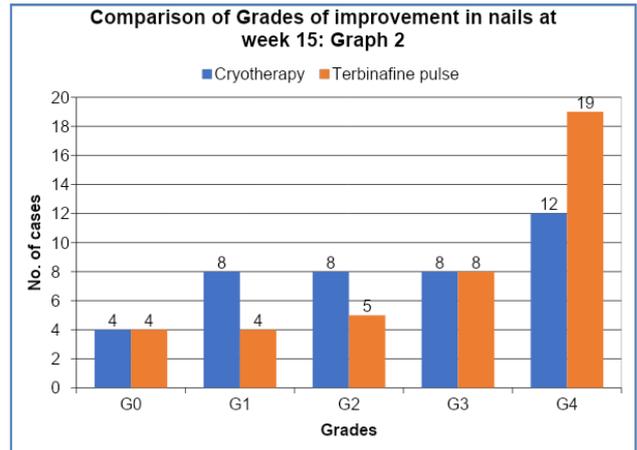


Figure 2: Comparison of grades of improvement in nails at week 15.

P value: 0.114 (insignificant)

In our study females outnumbered males in ratio of 2.3:1, with a prevalence of 70% in females and 30% in males.

Most of the subjects in our study belonged to the rural population i.e. 49 out of 80, while (31 out of 80) belonged to the urban population. Majority of our patients were housewives (40%), and least affected were businessmen (2.5%) and skilled labourers (2.5%). Maximum number of patients in our study had fingernail onychomycosis for duration of <2 years, with a mean duration of 1.5 years. Distal lateral type of onychomycosis was the most commonly encountered clinical type and only 10% of patients in our study group had concurrent cutaneous involvement. Microscopic examination with potassium hydroxide revealed fungal elements in 62.5% of our patients.

Comparison of grades, of improvement in nails treated with cryotherapy and oral terbinafine pulse during the follow-up period are depicted in Figure 1-5.

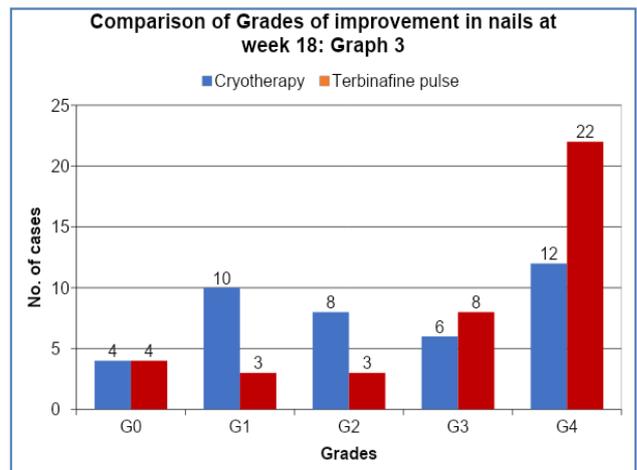


Figure 3: Comparison of grades of improvement in nails at week 18.

P value: 0.17(significant)

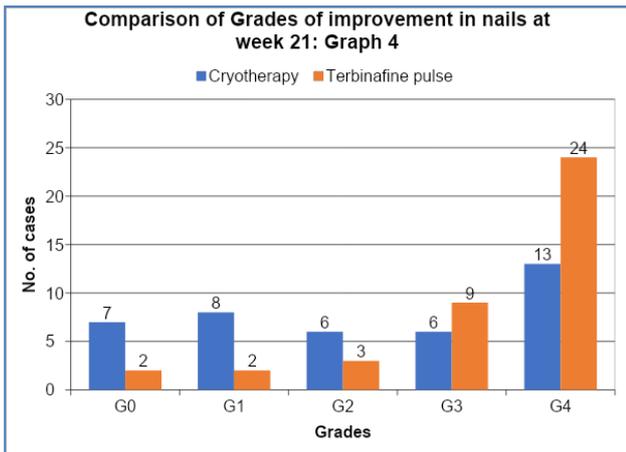


Figure 4: Comparison of grades of improvement in nails at week 21.

P value: 0.002 (significant)

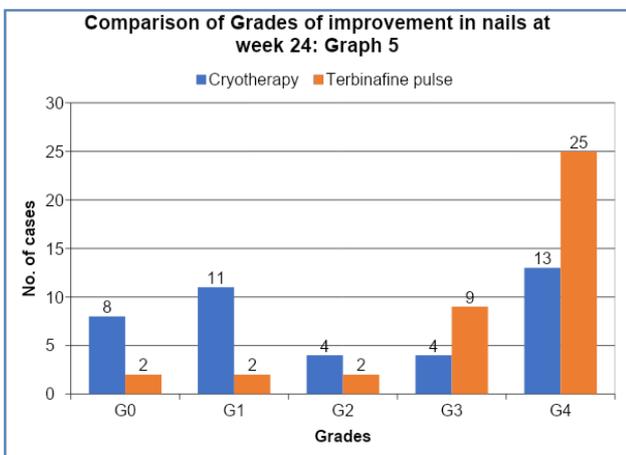


Figure 5: Comparison of grades of improvement in nails at week 24.

P value:0.001 (significant)

DISCUSSION

Our study evaluated the different clinical types of onychomycosis and their response to either oral terbinafine pulse therapy or cryotherapy with liquid nitrogen. A total of 80 patients with fingernail onychomycosis were evaluated in our study. The age of the patients ranged between 20 to 75 years. The maximum age of the patient seeking treatment was 60 years and the minimum age enrolled was 20 years. More than 50% of the subjects, i.e. 53 out of 80 belonged to the age group of 21 to 40 years. Majority of the patients (33/80) belonged to the age interval of 31 to 40 years, with the number of patients decreasing towards the extremes. Lower incidence of onychomycosis in children is supported by a study by Gupta et al.⁵ This has been attributed to reduced exposure to fungus, faster nail growth and smaller nail surface for invasion. We observed onychomycosis in only 10% of the patients in elderly age group (51-60 years). This was in

contradiction to Elewski et al who reported onychomycosis in 28.1% of the patients aged 60 years or older.⁶ Reasons for such contradictory results between two studies can be exclusion of patients with toenail onychomycosis from our study and decreased health care concerns in elderly age group in our population.

Among the subjects having fingernail onychomycosis, females outnumbered males in ratio of 2.3:1, with a prevalence of 70% in females and 30% in males. This is conformity with study by Sigurgeirsson et al in 2002.⁷ Bramono et al in 2005 also reported female preponderance with a ratio of 1.5:1 to 2:1.⁸ However Elewski et al reported onychomycosis in 6.5% of females and 13.3% of the males which was contradictory to our study.⁸

Most of the subjects in our study belonged to the rural background i.e. 49 out of 80 patients making 61.3% of the total subjects evaluated, while 38.8% belonged to the urban population. This can be because of greater exposure to fungus in relatively damp rural environments and declining health of subjects in rural populations.

The occupation profile of the subjects in our study was varied, with patients belonging to different walks of life reporting for their nail disease. Majority of patients were housewives (40%) and farmers (25%), followed by unskilled labourers, students (11.25%), servicemen (6.25%) and least affected were businessmen (2.5%) and skilled labourers (2.5%). This observation reflects that fingernail onychomycosis has a significant functional and psychosocial impact upon different professional and socio-economic strata. The higher incidence among housewives is because of repeated exposure to a damp environment leading to perpetuation of infection by pathogenic fungi. Farmers and unskilled labourers too have higher incidence of finger nail onychomycosis due to greater exposure to the saprophytic fungi in the soil, excessive perspiration and also because of greater day to day occupational work and trauma predisposing to increased risk of fungal invasion in the deformed nail. Several studies have considered that onychomycosis adversely affects the quality of life, resulting in impaired function due to pain and loss of dexterity.⁹

Most of the subjects (61.25%) in our study had onychomycosis for a duration of less than 2 years, with a mean duration of 1.5 years. 37.5% suffered from onychomycosis for a duration of 2 to 5 years. Minimum and maximum duration of affection was 2 months and 5 years respectively. Younger age group and female patients reported earlier for their nail disease. Mean number of fingernails affected was 4.215 with minimum and maximum affected nails being 1 and 10 respectively.

On evaluation of patterns of onychomycosis, distal lateral pattern was the most common pattern observed in our study (81.25%). Other clinical patterns found were candidal onychomycosis (15%) and total dystrophic

onychomycosis (3.75%). None of our patients in the study group had proximal subungual or white superficial onychomycosis. This is in contrast to study by Satpathi et al who reported proximal subungual onychomycosis in 15.7% of the subjects and white superficial onychomycosis in 10.8% of the patients.¹⁰

Concomitant cutaneous involvement was observed in 10% of patients in our study group. 5% of the patients had *Tinea cruris* and 2.5% of the patients had *Tinea corporis*. *Tinea manuum* was present in only 1.25% of the subjects and that too with total dystrophic type of onychomycosis. Patients with concomitant cutaneous involvement had greater duration of onychomycosis. This is in contrast with study by Asadi et al who reported concomitant *Tinea pedis* in 34.6% of the patients affected by toenail onychomycosis.¹¹

Amongst the 80 cases included in our study it was observed that a total of 50 clinically suspected onychomycosis patients were confirmed by direct KOH examination. This was higher than study by Satpathi et al who reported confirmation in 39.7% of the subjects by 20% KOH examination.¹⁰

At the end of our study, out of 80 patients with fingernail onychomycosis, 32.5% (13/40) of the patients achieved grade 4 response which was considered as clinical cure in group 1, in contrast 62.5% (25/40) of the patients treated with oral terbinafine pulse achieved clinical cure. And greater than 50% improvement i.e., G3 response was seen in 10% of the patients in Group 1 and 22.5% of the patients in group 2. The results at 24 weeks were in contrast with those observed at 12 weeks. At 12 weeks 40% of the patients in group 1 achieved clinical cure which was comparable to treatment with oral terbinafine pulse which was 45% and G3 response was attained by 20% of the patients in Group 1 and 17.5% patients in group 2. The results at 12 weeks were comparable in two groups and p value was insignificant. (Figure 1-5) with increase in duration a greater response was seen in Group 2 as compared to group 1. This was attributed to persistence of terbinafine in nails for a longer duration (6 months) while the effect of cryotherapy with liquid nitrogen was short lived and the effect of cryotherapy waned with time. Therefore the results with cryotherapy were inferior to those of terbinafine. Results in our study were supported by Valkova et al who reported marked improvement with oral terbinafine pulse in finger nail onychomycosis.¹² While a study by Warshaw et al reported superiority of continuous dose terbinafine over pulse dose of terbinafine in toenail onychomycosis.¹³

Cryotherapy has not been evaluated for its role in treatment of onychomycosis, although it has proved to be an effective, simple and safe therapeutic option in treating subcutaneous mycoses by several studies.¹⁴⁻¹⁷ Inferiority of results in our study could be attributed to shorter duration of treatment with cryotherapy and decreased penetration of liquid nitrogen through

subungual hyperkeratosis which could have served as a reservoir for the pathogenic fungi so that infection got re-established with weaning off of the effect of cryotherapy.

No serious complications of either of the two treatment modalities were seen in our study. Pain during the procedure was the most common side effect of cryotherapy, observed in 25 out of 40 patients however, it was mild to moderate in intensity and persisted for only a few hours after the procedure. Formation of subungual hematoma was observed in 4 out of 40 patients treated with cryotherapy. The local side effects observed were transient in nature and resolved completely over time, without any serious consequences. There was no limitation of daily life activities, even immediately after the procedure. Oral terbinafine pulse was well tolerated with headache experienced by 10% of the patients, but it was mild in intensity and resolved without any need for medications. Transient elevation in liver function tests was observed in 5% of the patients but returned to baseline after completion of treatment. Only cutaneous side effect observed was pruritus which was relieved with anti-histamines taken as and when required. Other minor adverse effects were diarrhea and dyspepsia which were more during the first week of pulse therapy. None of the adverse effects required discontinuation of treatment.

CONCLUSION

Thus, to conclude, overall results of cryotherapy were inferior to oral terbinafine pulse. Though, results with cryotherapy were comparable to oral terbinafine pulse at 12 weeks, at 24 weeks oral terbinafine pulse proved to be a treatment option in fingernail onychomycosis. Inferiority of results in our study could be attributed to shorter duration of treatment with cryotherapy and decreased penetration of liquid nitrogen through subungual hyperkeratosis which could have served as a reservoir for the pathogenic fungi so that infection got re-established with weaning off of the effect of cryotherapy.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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