

Comparative Study Between Pulsed and Continuous Itraconazole for the Treatment of Onychomycosis

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ABSTRACT

Objective: To compare efficacy of pulsed versus continuous daily oral Itraconazole in the treatment of onychomycosis.

Study Design: Randomized Control Trial (ClinicalTrials.gov: NCT05567484).

Place and Duration of Study: Department of Dermatology, Combined Military Hospital, Abbottabad, Pakistan, from May to Dec 2021.

Methodology: We enrolled 60 patients whose toenails showed signs of onychomycosis (crumbling nail plates, thicker nail beds, and yellowing). They were randomly divided into Group-A and Group-B, with 30 patients each. Group -A (Pulse Therapy) took two capsules of oral Itraconazole 100 mg twice weekly for one week every month for three months while Group-B (Continuous Therapy) received continuous oral 100 mg of Itraconazole once daily for 12 weeks continuously. Patients were subjected to an Onychomycosis Severity Index-based clinical evaluation.

Results: In Group-A (Pulse Therapy), 25(83.3%) patients showed mycological cure whereas in Group-B (Continuous Therapy), 23(76.7%) patients showed mycological cure but difference in the efficacy of both drugs was not statistically significant (p -value=0.519).

Conclusion: Pulsed therapy with Itraconazole and continuous Itraconazole therapy have comparable efficacies in treating dermatophyte toenail onychomycosis.

Keywords: Continuous Itraconazole Therapy, Fungal Infection, Onychomycosis, OSI (onychomycosis severity index), Pulsed Therapy.

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INTRODUCTION

Onychomycosis is a fungal infection of the toenails or fingernails that may involve any component of the nail unit, including the matrix, bed, or plate, leading to pain, discomfort, and disfigurement and may produce serious physical and occupational limitations, as well as reducing quality of life.¹ An extensive literature search revealed that the dermatophytes *Trichophyton mentagrophytes* and *Trichophyton rubrum* are responsible for 90% cases of onychomycosis in the toenails and 75% cases in the fingernails,² with co-occurring conditions such diabetes mellitus, peripheral vascular disease, and immunosuppression due to HIV increasing the risk of adverse outcomes.³ Onychomycosis of mycological cure is treated with Itraconazole, but its therapeutic value is still debated, even though a previous study found no significant superiority of continuous Itraconazole 200 mg once day for 12 weeks

as one study reported, 88.2% mycological cure at week 48, in the pulse Itraconazole group while another study reported 56.50% mycological cure rate for continuous Itraconazole.^{4,5} This study will strengthen the scant information about the efficacy of pulsed and continuous Itraconazole in the treatment of onychomycosis in our local population, where conflicting results have been reported previously.

METHODOLOGY

The randomized controlled trial (ClinicalTrials.gov: NCT05567484) was conducted at the Department of Dermatology, Combined Military Hospital (CMH), Abbottabad, Pakistan, from May 2021 to December 2021. The study began after gaining permission from Ethics Review Board (Reg CMH Atd-ETH-27-Derm-22). The sample of 60 patients was calculated using WHO sample size calculator taking 88.2%,⁴ proportion of mycological cure rate for pulse Itraconazole and 56.50%,⁵ mycological cure rate for continuous Itraconazole using nonprobability consecutive sampling technique. Patients were randomly assigned into two groups (30 patients in each group) using blocked randomization.

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Inclusion Criteria: Patients of either gender, aged 20-60 years with direct microscopy evidence of fungus (hyphae or blastospores on the infected toenail and a positive fungal culture) with no previous treatment history were included.

Exclusion Criteria: Subjects who were pregnant, breastfeeding, or who intended to become pregnant during the trial, patients with a history of oral Itraconazole allergy or renal illness and baseline levels of liver enzymes (ALT, AST, alkaline phosphatase, and total bilirubin) that were more than twice the upper limit of normal and patients with ischemic heart disease and congestive heart disease were excluded.

Patients were placed in either Group-A or Group-B using block randomization (Figure). Patients in Group-A (Pulse Therapy) took two capsules of oral Itraconazole 100 mg twice weekly for one week every month for three months while patients in Group-B (Continuous Therapy), received continuous oral 100 mg of Itraconazole once daily for 12 weeks. Before and during the administration of drugs, baseline LFTs and RFTs were also monitored for safety of therapy. At the end of second, and third months, mycological cure was used to establish efficacy in both groups (negative fungal direct microscopy and negative fungal culture).

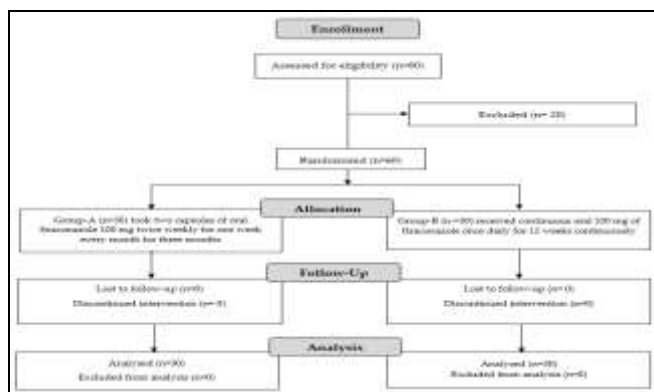


Figure: Patient Flow Diagram (n=60)

Data was analyzed using Statistical Package for Social Sciences (SPSS) Software version 23.0. Frequencies and percentages were calculated for categorical variables. Chi-square test was applied keeping *p*-value of <0.05 as statistically significant.

RESULTS

We included 60 patients (30 patients in each group) in the study. In Group-A (Pulse Therapy), 21(70%) patients were recorded in 41-60 years age group while in Group-B (Continuous Therapy),

19(63.3%) patients were recorded in 41-60 years age group. In Group-A (Pulse Therapy), there were 19(63.3%) male patients and 11(36.7%) female patients while in Group-B (continuous therapy), there were 17(56.7%) male patients and 13(43.3%) female patients. Further demographic information is listed in Table-I. As per efficacy in Group-A (pulse therapy), 25(83.3%) patients achieved mycological cure while in Group-B (continuous therapy), 23(76.7%) patients achieved mycological cure, as shown in Table-II.

Table-I: Demographic Data of Patients (n=60)

Demographic Variables	Study Groups		p-value
	Group-A (n=30) n(%)	Group-B (n=30) n(%)	
Age Groups			
20-40 Years	09(30.0%)	11(36.7%)	0.583
41-60 Years	21(70.0%)	19(63.3%)	
Gender			
Male	19(63.3%)	17(56.7%)	0.598
Female	11(36.7%)	13(43.3%)	

Table-II: Efficacy of Pulsed and Continuous Itraconazole for the Treatment of Onychomycosis in Both Groups (n=60)

Efficacy	Study Groups		p-value
	Group-A (n=30) n(%)	Group-B (n=30) n(%)	
Yes	25(83.3%)	23(76.7%)	0.519
No	05(16.7%)	07(23.3%)	

DISCUSSION

Patients in our experiment followed similar protocols as another study which corroborated our findings. 6 Another trial found no difference in mycological cure,⁷ between continuous Terbinafine 250 mg daily for 12 weeks, 16 weeks, or 24 weeks; pulsed terbinafine 500 mg; weekly Fluconazole; or pulsed and continuous Itraconazole. While previous studies have produced conflicting findings,⁸ this study was planned to evaluate pulsed and continuous Itraconazole for the treatment of onychomycosis. Although topical antifungal agents (Amorolfine, Ciclopirox) have been shown to be effective against onychomycosis, most clinicians have recommended oral treatment with terbinafine (in the case of a dermatophyte infection), fluconazole (in the case of a yeast infection), or Itraconazole,⁹ if more than half of the nail plate is affected. Our findings contrasted with the results of Li *et al.*¹⁰ who reported 41% versus 91% mycological cure between pulsed and continuous Itraconazole of the target toenail.

Studies have shown that Terbinafine has a 76% mycological cure rate, Itraconazole pulse dosing has a 63% mycological cure rate, and fluconazole has a 48% mycological cure rate; Itraconazole topical therapy has a 55% mycological cure rate, and Tavaborole or Ciclopirox have a 36% mycological cure rate,^{11,12,13} similar to our findings. Patients treated with continuous Itraconazole 200 mg achieved mycological cure significantly more often than those treated with topical treatments in another randomized controlled trial,¹⁴ however, mycological cure was not significantly more likely to be achieved with fluconazole, pulse regimens of Terbinafine and Itraconazole, or topical treatments. Although oral Itraconazole has been found to be the most effective treatment for onychomycosis in numerous studies, topical monotherapy may be an appropriate therapeutic alternative for mild to moderate onychomycosis in patients for whom oral antifungal drugs are either ineffective or intolerable.¹⁵⁻¹⁷

Onychomycosis is currently treated with what are regarded to be the gold standard pharmacological therapies; nevertheless, studies,¹⁸⁻²² have revealed low success rates with rising antifungal treatment resistance. One study,²³ found that continuous Terbinafine was more effective than intermittent Itraconazole, in achieving a definitive mycological cure of toenail onychomycosis.

LIMITATION OF STUDY

Small sample size and selective nature of this research due to its study design were the main limitations due to which results cannot be generalized to overall population.

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CONCLUSION

Pulsed therapy with Itraconazole and continuous Itraconazole therapy have comparable efficacies in treating dermatophyte toenail onychomycosis.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

RR & MH: Conception, study design, drafting the manuscript, approval of the final version to be published.

BM & NA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MAS & KA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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