DOI: https://doi.org/10.53350/pjmhs20221612745

ORIGINAL ARTICLE

Comparative Study Between Pulse Therapy with Oral Itraconazole Versus Continuous Oral Terbinafine Therapy for Treatment of Onychomycosis

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ABSTRACT

Objective: The purpose of this study is to evaluate the efficacy of onychomycosis treatment using pulses of oral itraconazole vs continuous dosing with oral terbinafine.
Study Design: Randomized Control Trial
Place and Duration of Study: Department of Dermatology, Combined Military Hospital, Abbottabad from 01 Mar, 2022 to 01 Aug, 2022.
Methodology: A total of 100 patients were included in this research study who were divided in two groups through blocked randomization and were enrolled through nonprobability consecutive sampling technique. Data was collected, entered, and analyzed using SPSS Version 23.0.
Results: In oral itraconazole (pulse therapy) group, 43 (86.0%) patients showed effective results while in oral terbinafine (continuous therapy) group, 32 (64.0%) showed effective results. P Value = 0.011.
Conclusion: This study demonstrated that oral itraconazole (pulse therapy) is significantly superior to oral terbinafine (continuous therapy) group in the treatment of treatment of onychomycosis.
Keywords: Onychomycosis, Fungal Infection, Pulsed Therapy, Continuous Itraconazole Therapy.

INTRODUCTION

Onychomycosis, sometimes known as nail fungus, may manifest itself on either the fingernails or toenails. Onychomycosis-causing fungi may invade the nail at three different points: the matrix, the nail bed, and the nail plate [1]. Can while onychomycosis isn't usually fatal, it may be exceedingly irritating and even prevent normal activities. It is important not to discount the impact that onychomycosis has on patients' emotional and social well-being [2].

Some of the most prevalent forms of onychomycosis include white superficial onychomycosis, proximal subungual onychomycosis, endonyx onychomycosis, and candidal onychomycosis. Sometimes, a patient's symptoms may fit into more than one category. The medical term for a severe case of onychomycosis is total dystrophic onychomycosis [3].

Onychomycosis comes in many forms, each with its own set of symptoms and probable causes. The most common kind of onychomycosis, known as distal lateral subungual onychomycosis, develops when a fungus travels up the nail from the plantar surface to the hyponychium and then into the nail bed [4].

The infection of the distal lateral and subungual parts of the nail is what defines distal lateral subungual onychomycosis. However, white superficial onychomycosis is more unusual and is caused by an invasion of the nail plate's surface [5]. Caused by fungal colonization of the subungual space under the proximal nail plate, proximal subungual onychomycosis is a very rare disorder. Endonyx onychomycosis occurs when fungi penetrate the epidermis and infect the nail plate [6]. Several clinical investigations have demonstrated that terbinafine is more effective than other antifungal medications. A review of 18 trials found that terbinafine had a much greater mycological cure rate for onychomycosis (76% vs. 63%) than either pulse itraconazole or fluconazole 50% vs 48% [7]. This investigation is to evaluate the efficacy of pulse therapy for the treatment of onychomycosis in comparison to that of oral itraconazole and continuous oral terbinafine.

METHODOLOGY

This was a randomized control trial carried out on 100 patients (50 patients in each group) through nonprobability consecutive sampling technique. This research was carried out at the Department of Dermatology, Combined Military Hospital, Abbottabad from 01 Mar, 2022 to 01 Aug, 2022 after taking approval form Hospital's Ethical Review Board (Ref: CMHAtd-ETH-37-Derm-22). Patients presented to Skin OPD of our hospital with complaint of toenail problem and meeting inclusion criteria were enrolled.

Inclusion Criteria: Participants were allowed if they were between the ages of 18 and 60, and their diagnosis of dermatophyte onychomycosis was validated by mycological culture.

Exclusion Criteria: Patients were not accepted if they had less than a 25% infection rate in one toenail, had impaired liver or renal function, were pregnant or nursing, or had a history of recurrent infections.

All study participants received a thorough briefing and signed an informed consent form prior to the start of the research. Onychomycosis patients received continuous terbinafine or pulse itraconazole (200 mg twice day, 1 week on, 3 weeks off, for 12 weeks) (250 mg once day, for 12 weeks). After 48 weeks of follow-up, mycological cure rate (negative KOH and culture) and effective cure were the main indicators of effectiveness (mycological cure plus nail plate involvement of 10 percent or less). The researcher personally conducted the data collection, under the guidance of a consultant dermatologist having at least seven years of experience beyond fellowship.

RESULTS

In oral itraconazole (pulse therapy), mean and SDs for age was 37.89+10.41 years. Mean and SDs for duration of disease was 3.30+1.21 months. In oral terbinafine (continuous therapy) group, mean and SDs for age was 35.56+8.99 years. Mean and SDs for duration of disease was 3.32+1.26 months. A total of 32 patients receiving oral itraconazole (pulse treatment) were young adults (aged 18–40), whereas 18 patients were middle-aged (aged 41–50). Of the patients using oral terbinafine (continuous group), 39 (78.0%) were between the ages of 18 and 40, while 11 (22.0%) were between the ages of 41 and 60. The significance level is 0.122. The gender breakdown of the oral itraconazole (pulse treatment) group was as follows: 28 (56.0%) male patients, 22 (44.0%) female patients. Thirty-one men (62.0%) and nineteen women (38.0%) were logged as patients in the oral terbinafine (continuous treatment) group. The corresponding probability value is 0.541.

In oral itraconazole (pulse therapy) group, 43 (86.0%) patients showed effective results while in oral terbinafine (continuous therapy) group, 32 (64.0%) showed effective results. P Value = 0.011.

In oral itraconazole (pulse therapy) group, 25 (58.1%) showed effective results while in 41-60 years age group, 18 (41.9%) patients showed effective results. P Value = 0.032. In oral

terbinafine (continuous therapy) group, 26 (81.3%) patients showed effective results while in 41-60 years age group 06 (18.8%) patients showed effective results. P Value = 0.459. (Table No. 1). In oral itraconazole (pulse therapy), 22 (51.2%) male patients while 21 (48.8%) female patients showed effective results. P Value = 0.088. In oral terbinafine (continuous therapy) group, 18 (46.3%) male patients' while 14 (43.8%) female patients showed effective results. P Value = 0.264. (Table No. 2). In oral itraconazole (pulse therapy) group, 30 (69.8%) patients presented with < 3 months duration of disease showed effective results while 13 (30.2%) patients presented with > 3 months duration of disease showed effective results. P Value = 0.005. In oral terbinafine (continuous therapy) group, 21 (65.6%) patients presented with < 3 months duration showed effective results while 11 (34.4%) presented with > 3 months duration of disease showed effective results. P Value 0.279. (Table No. 3).

Table-1: Stratification of Efficacy with Age Groups (n=100)

Treatment Groups			Age Group		Total	P Value
			18-40 Years	41-60 Years		
Oral Itraconazole (Pulse Therapy) (n=50)	Efficacy	Yes	25	18	43	0.032
			58.1%	41.9%	100.0%	
		No	7	0	7	
			100.0%	0.0%	100.0%	
	Total		32	18	50	
			64.0%	36.0%	100.0%	
Oral Terbinafine (Continuous Therapy) (n=50)	Efficacy	Yes	26	6	32	0.459
			81.3%	18.8%	100.0%	
		No	13	5	18	
			72.2%	27.8%	100.0%	
	Total		39	11	50	
			78.0%	22.0%	100.0%	

Table-2: Stratification of Efficacy with Gender (n=100)

Treatment Groups			Gender		Total	P Value
			Male	Female		
Oral Itraconazole (Pulse Therapy) (n=50)	Efficacy	Yes	22	21	43	0.088
			51.2%	48.8%	100.0%	
		No	6	1	7	
			85.7%	14.3%	100.0%	
	Total		28	22	50	
			56.0%	44.0%	100.0%	
Oral Terbinafine (Continuous Therapy) (n=50)	Efficacy	Yes	18	14	32	0.264
			56.3%	43.8%	100.0%	
		No	13	5	18	
			72.2%	27.8%	100.0%	
	Total		31	19	50	
			62.0%	38.0%	100.0%	

Table-3: Stratification of Efficacy with Duration of Disease (n=100)

Treatment Groups			Duration of Disease		Total	P Value
			< 3 Months	> 3 Months		
Oral Itraconazole (Pulse Therapy) (n=50)	Efficacy	Yes	30	13	43	0.005
			69.8%	30.2%	100.0%	
		No	1	6	7	
			14.3%	85.7%	100.0%	
	Total		31	19	50	
			62.0%	38.0%	100.0%	
Oral Terbinafine (Continuous Therapy) (n=50)	Efficacy	Yes	21	11	32	0.279
			65.6%	34.4%	100.0%	
		No	9	9	18	
			50.0%	50.0%	100.0%	
	Total		30	20	50	
			60.0%	40.0%	100.0%	

DISCUSSION

Terbinafine, or another antifungal medicine, is a viable treatment option. [8-11]. Drug-induced lupus erythematosus, Sjogren's disease, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, and psoriasis are some examples of adverse reactions have all been reported as individual terbinafine side effects [12-14]. Some of the less severe adverse effects of terbinafine include skin itchiness or hives, headaches, or muscular discomfort. Patients with onychomycosis received either oral terbinafine or oral itraconazole (pulse treatment; 200 mg twice day, 1 week on, 3 weeks off, for 12 weeks) (continuous therapy; 250 mg once daily, for 12 weeks).

Onychomycosis patients were randomised to either oral terbinafine or oral itraconazole (pulse treatment; 200 mg twice daily, 1 week on, 3 weeks off, for 12 weeks) (continuous therapy; 250 mg once daily, for 12 weeks). In the current study, in oral itraconazole (pulse therapy) group, 43 (86.0%) patients showed effective results while in oral terbinafine (continuous therapy) group, 32 (64.0%) showed effective results. P = 0.011. In oral itraconazole (pulse therapy) group, 25 (58.1%) showed effective results while in 41-60 years age group, 18 (41.9%) patients showed effective results. P Value = 0.032. In oral terbinafine (continuous therapy) group, 26 (81.3%) patients showed effective results while in 41-60 years age group 06 (18.8%) patients showed effective results. P = 0.459. In oral itraconazole (pulse therapy), 22 (51.2%) male patients while 21 (48.8%) female patients showed effective results. P = 0.088. In oral terbinafine (continuous therapy) group, 18 (46.3%) male patients' while 14 (43.8%) female patients showed effective results. P Value = 0.264. In oral itraconazole (pulse therapy) group, 30 (69.8%) patients presented with < 3 months duration of disease showed effective results while 13 (30.2%) patients presented with > 3 months duration of disease

showed effective results. P Value = 0.005. In oral terbinafine (continuous therapy) group, 21 (65.6%) patients presented with < 3 months duration showed effective results while 11 (34.4%) presented with > 3 months duration of disease showed effective results. P Value 0.279. (Table No. 7). According to the results of the Zaias study [20], onychomycosis caused by T. rubrum is best treated with a 250 mg quarterly terbinafine regimen pulse. Additional study with a larger sample size is required to assess the effectiveness of the trimester schemes of oral terbinafine in treating all kinds of dermatophyte onychomycosis.

Onychomycosis treatment outcomes may be impacted by patient factors such as age, clinical presentation, comorbidities, and the use of drugs that may interfere with antifungal therapy. In our study, the mean age of oral itraconazole (pulse treatment) patients was 37.89 years, with a standard deviation of 10.41 years. A person with the illness typically has it for 3.30+1.21 months. The average age of subjects who regularly took terbinafine orally was 35.56 years old, with an 8.99-year standard deviation. A typical hospitalisation lasted 3.32 months on average, with a 1.26-month range. It was noted that 32 people between the ages of 18 and 40 and 18 patients between the ages of 41 and 50 used oral itraconazole (pulse treatment). The greatest age group of individuals who used oral terbinafine (78.0%) was between the ages of 18 and 40, followed by those in the 41–60 age range (22.0%). P value for it is 0.122.

Despite this study's limitations, significant associations were found between outcomes and clinical presentation, the presence of comorbidities, and the usage of concomitant drugs. Most likely the small sample size. According to a study21, at week 48, 88% (30/34) of patients treated with itraconazole and 79% (23/29) of patients treated with terbinafine had achieved mycological cure (P not significant). There was a successful cure in 52.9 percent (18/34) of the itraconazole group and 51.7 percent (15/29) of the terbinafine group (mycological cure with or more than 10% nail plate involvement) (P not significant). However, as compared to the findings of this study where in oral itraconazole (pulse therapy) group, 43 (86.0%) patients showed effective results while in oral terbinafine (continuous therapy) group, 32 (64.0%) showed effective results. P = 0.011.

Itraconazole had a 90% mycological cure rate and an 82% clinical cure rate, whereas terbinafine had a 79% clinical cure rate and an 87% mycological cure rate, according to a different study22. In this case, there was no discernible difference between the two groups. Notably, three people using itraconazole reported stomach issues. No significant adverse events occurred, and no drug interactions were reported [15-17]. Headaches, viral infections, and nausea were the most common negative effects seen by people in both groups. There was no research that looked at recurrence rate to include in this evaluation. When compared to oral itraconazole, oral terbinafine may improve cure rates while also causing fewer side effects. The frequency of occurrence was only evaluated in four contrasts: There is some indication that terbinafine, and azoles reduce the recurrence rate compared to placebo, but the evidence is weak and there may be no difference between the two. Few research recorded negative outcomes, and the severity of those that were reported was not considered [18-20].

In conclusion, despite the small sample size, this study found that the oral itraconazole (pulse therapy) group fared better than the oral terbinafine (continuous therapy) group when treating onychomycosis, with the latter group administering 250 mg of terbinafine once day for 12 weeks. More extensive investigations with a larger sample size are needed to verify the efficacy of this treatment plan in our community.

Acknowledgement: Brig Anjum Anwar Qadri

Limitations of Study: The study's biggest flaw was its limited sample size, and as it was conducted in just one location, its findings cannot be extrapolated to the whole region.

CONCLUSION

This study demonstrated that oral itraconazole (pulse therapy) is significantly superior to oral terbinafine (continuous therapy) group in the treatment of treatment of onychomycosis. Further large multicentered randomized control trials shall be carried out across the province of KP in order to generalize results to overall population by confirming both regimen's effectiveness.

Conflict of interest: None

Authors contribution: MA: Design the study, MH: analysis and interpretated result, BM: Data interpretation, manuscript writing, revision and approval of manuscript, NA: Coordinated, supervised data collection, and approval of final manuscript.

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