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Efficacy and Safety of Combination Treatment of Oral Terbinafine and Itraconazole in Patients with Extensive Superficial Dermatophytes

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ABSTRACT

Background: Dermatophytosis, a prevalent fungal infection, is instigated by species like Trichophyton, Epidermophytonand Microsporum. The current approach for treating dermatophytosis involves a blend of systemic and topical antifungal therapies, applicable to all patients except those with localized, untreated Tinea. Notably, there is a growing incidence of inadequate response to the standard treatment regimen in recent times.

Objective: To evaluate the efficacy andsafety of combination treatment of oralterbinafine anditraconazole in patients with extensive superficial dermatophytes.

Materials and Methods: This research comprised a randomized clinical trial involving 50 individuals diagnosed with extensive superficial dermatophytosis. Study conducted at the Department of Dermatology and Venereology, Combined Military HospitalCumilla, the study spanned from July 2022 to June 2023. During the six-week duration, patients underwent treatment with terbinafine and itraconazole, with follow-up examinations every two weeks, including relevant investigations. Evaluation of treatment outcomes occurred at both four and six weeks. Statistical analysis was performed using version 25 of the Statistical Package for the Social Sciences (SPSS).

Results: This study shows the majority of the participants within the age range of 16-30 years (56.0%) and the average age of the participants is 31.74±11.77 years. In terms of gender, the majority are male (78.0%). The most prevalent diagnosis is Tinea corporis (68.0%), followed by Tinea cruris (36.0%), Tinea faciei (28.0%), and Tinea incognito (12.0%). The majority of participants (85.0%) have had the disease for 12 months or less. The most common sites are the trunk (35.0%), whole body (26.0%), and crural area (24.0%). The majority of participants experience severe itching (56.0%), followed by moderate itching (34.0%), and a smaller percentage report mild itching (10.0%). The majority of participants showed improvement, with percentages increasing from 66.0% after 2 weeks to 84.0% after 4 weeks.The percentage of cured individuals also increased over time, reaching a substantial 90.0% after 6 weeks.

Conclusion: The amalgamation of terbinafine and itraconazole demonstrates a superior clinical cure rate compared to use of single systemic antifungals. However, the observed clinical cure rate percentage is lower when juxtaposed with findings from previous studies. Notably, neither combination of systemic antifungals has exhibited efficacy against tinea infections previously treated with formulations containing topical steroids.

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Introduction

Dermatophytosis stands out as a prevalent skin ailment with a global impact, resulting from superficial fungi infiltrating and proliferating within keratinized tissues such as the skin, hair, and nails. Tinea, the condition associated with dermatophytosis, affects approximately 20-25% of the world population [1,2]. Over the past four decades, notable progress has been made in managing this condition, evolving from basic antiseptics with nonspecific antifungal properties to the specialized antifungal medications available today [1,3].

The primary fungi responsible for dermatophytosis include Trichophyton, Microsporum, and Epidermophyton [1,4]. Recently, there has been a shift in the tinea pattern, characterized by an increase in the prevalence of challenging-to-treat conditions such as recalcitrant, recurrent, and chronic dermatophytosis [3,5]. Several factors contribute to the emergence of treatment-resistant tinea, including global warming, hot and humid climates, labor migration, frequent use of tight and synthetic clothing, obesity, sedentary lifestyles, the rising prevalence of Trichophytonmentagrophytes, and poor patient compliance[1,6,7]. Another significant contributor is the widespread misuse of topical

steroid-antifungal combination creams, often acquired over the counter or prescribed by practitioners or unauthorized individuals [8].

Terbinafine, the primary systemic drug for dermatophytosis, operates as a first-line treatment by inhibiting squaleneepoxidase, an enzyme involved in ergosterol synthesis crucial for fungal cell membrane formation [9].Itraconazole exerts fungistatic action by inhibiting 14α-demethylase, thereby hindering fungal cell wall synthesis [10].

Utilizing a combination therapy involving systemic antifungal drugs with distinct mechanisms of action has been shown to improve cure rates and mitigate drug resistance, relying on the synergistic and additive effects of multiple drugs [1]. The effectiveness of both itraconazole and terbinafine in managing dermatophyte infections has been documented in several studies [7,11-13]. From a clinical perspective, it becomes crucial for clinicians to assess the comparative efficacy of these two drugs in standard clinical scenarios. Consequently, the present study was designed to assess the safety and efficacy of a combined treatment involving terbinafine and itraconazole in patients with extensive superficial dermatophytes.

Materials and Methods

A non-blinded randomized clinical trial was conducted involving 50 extensivedermatophytosis patients attending the Outpatient Department (OPD) of the Department of Dermatology and Venereology at Combined Military Hospital Cumilla from July 2022 to June 2023. The study included patients with Tinea corporis, Tinea cruris, and Tinea faciei,Tinea incognito with a total body surface area involvement of at least 50%. Exclusions comprised pregnant and lactating women, individuals allergic to terbinafine/itraconazole those with a history of oral antifungal intake in the last month, patients with cardiac, renal, and hepatic diseases, abnormal complete blood count, renal function test, and liver function test. Enrolled patients meeting the inclusion criteria provided informed consent before participation. The treatment involved administering terbinafine 250 mg and itraconazole 200 mg daily until lesion resolution or a maximum of 6 weeks. Patients were considered cured when there was an absence of scaling, erythema, and pruritus along with a negative KOH test.

Patients underwent evaluation for the severity of clinical parameters, specifically erythema, using a four-point scale: 0=none, 1=mild, 2=moderate, and 3=severe [1]. Initial, second-week, and fourth-week assessments included Complete Blood Count (CBC), Liver Function Test (LFT), and Electrocardiography (ECG) and CBC and LFT. Patients were queried about any treatment-related side effects. Follow-up occurred at two-week intervals for a maximum of eight weeks (four weeks post-therapy or cure, whichever came first). Monitoring encompassed the treatment period and an additional four weeks post-treatment completion. The 'Rule of 9' was used to calculate Body Surface Area (BSA). Outcome measurements included Cured (complete clinical resolution), Partially Cured (more than 50% improvement in involved total BSA), and Failure (increased severity or no improvement after four weeks of antifungal therapy or less than 50% involved total BSA improvement). Data analysis was performed using SPSS software version 25.

Results

The majority of the participants fall within the age range of 16-30 years (56.0%), followed by the age range of 31-45 years (34.0%). Only a small percentage are aged 46-60 years (6.0%), and there are even fewer participants above 60 years (4.0%). The average age of the participants is 31.74 years with a standard deviation of 11.77. In terms of gender, the majority are male (78.0%), and most participants are married (78.0%) (Table 1).

Table 1: Demographic Characteristics of the Study Subject (n=50)

Age in years	Frequency	Percentage (%)
16-30	28	56.0
31-45	17	34.0
46-60	3	6.0
>60	2	4.0
Mean±SD	31.74±11.77	
Sex		
Male	39	78.0
Female	11	22.0
Marital status		
Married	36	72.0
Unmarried	14	28.0

The most prevalent diagnosis is Tinea corparis (68.0%), followed by Tinea curis (36.0%), Tinea faciei (28.0%), and Tinea incognito (12.0%) (Figure 1).

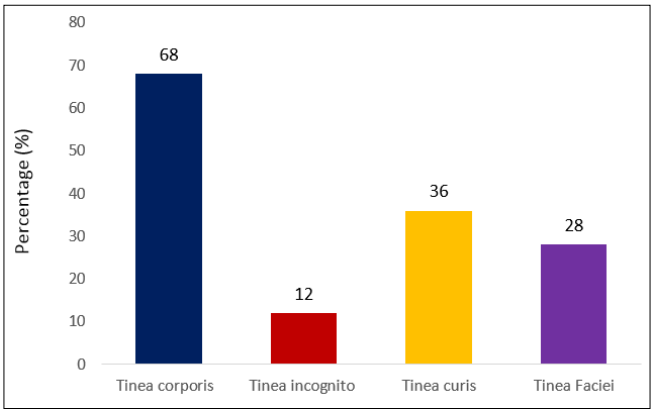

Figure 1: Diagnosis of Disease of the Study Subject (n=50)

The majority of participants (85.0%) have had the disease for 12 years or less, while a smaller percentage have had the disease for 1-3 years (8.0%) or more than 3 years (6.0%) (Table 2).

Table 2: Duration of Disease of the Study Subject (n=50)

Duration	Frequency	Percentage (%)
≤12 months	43	85.0
1-3 months	4	8.0
>3 months	3	6.0

The most common sites are the trunk (35.0%), whole body (26.0%), and genital area (24.0%). Other sites include the axilla, back of the chest, perioral region, buttock, left thigh, scrotum, face, growin axilla, neck & chest, hand and lower back (Table 3).

Table 3: Site of Disease of the Study Subject (n=50)

Site of disease	Frequency	Percentage (%)
Crural area	12	24.0
Whole body	13	26.0
Trunk	15	35.0
Axilla	11	22.0
Back of the chest	3	6.0
Perioral region	3	6.0
Buttock	3	6.0
Thigh	4	8.0
Scrotum	4	8.0
Face	6	12.0
Axilla	3	6.0
Neck & chest	2	4.0
Hand	1	2.0
Lower back	1	2.0

The majority of participants experience severe itching (56.0%), followed by moderate itching (34.0%), and a smaller percentage report mild itching (10.0%) (Figure 2).

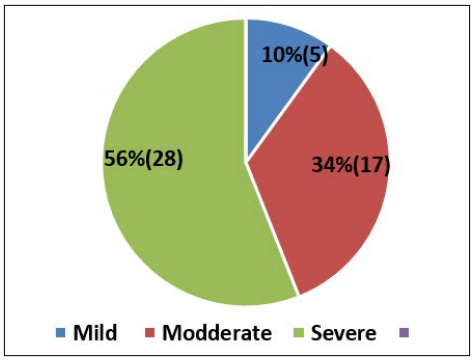

Figure 2: Itching of the Study Subject (n=50)

The majority of participants showed improvement, with percentages increasing from 66.0% after 2 weeks to 84.0% after 4 weeks.The percentage of cured individuals also increased over time, reaching a substantial 90.0% after 6 weeks (Table 4).

Table 4: Follow up of Study Subject (n=50)

Follow up	Frequency	Percentage (%)
After 2 weeks		
Improved	33	66.0
Not improve	14	28.0
Cured	3	6.0
After 4 weeks		
Improved	42	84.0
Not improve	3	6.0
Cured	5	10.0
After 6 weeks		
Improved	3	6.0
Not improve	2	4.0
Cured	45	90.0

This table indicates that 4.0% of the participants experienced elevated liver enzymes as a complication during the study (Table 5).

Table 5: Complication of the Study Subject (n=50)

Complication	Frequency	Percentage (%)
Elevated liver enzymes	2	4.0

Discussion

Dermatophytosis is a prevalent superficial mycosis on a global scale [7,14]. Numerous antifungal agents have been developed and more are in progress for treating this condition. Terbinafine stands out as one of the most widely employed antifungal drugs for superficial fungal infections due to its broad-spectrum fungicidal activity. The drug has consistently demonstrated efficacy against dermatophytes, that achieves cure rates exceeding 90% at a daily dose of 250 mg over a 2-week period [15].

However, recent observations note instances of clinical failure and relapses with terbinafine in patients with tinea infections, coinciding with an increased incidence of terbinafine resistance [16]. While resistance is not a common occurrence in case of terbinafine in clinical practice, a few authors have reported it in clinical isolates [6,7,8]. Majid et al. revealed in their study that only 43 out of 100 cases were able to maintain a long-term clinical and mycological cure after a 2-week oral terbinafine treatment, emphasizing the prevalence of incomplete mycological cure and relapse after standard terbinafine therapy for tinea corporis/cruris [16].

One of the primary mechanisms behind antifungal resistance is a decrease in effective drug concentration [17]. This phenomenon is well-established in terbinafine due to its standard dosing regimen of 250 mg daily, that causes accumulation of drug in skin and adipose tissue.9 This underscores that the current standard terbinafine therapy with a 250 mg/day dose may not be sufficient in the present context, where as resistance of fungus is exacerbated by increased usage, inappropriate prescribing, and over-the-counter sales of antifungal agents [10,11].

While there is no definitive evidence on the optimal strategy to prevent resistance, historically, the most commonly recommended measures have included the judicious use of antifungals and appropriate dosing, with a specific emphasis on avoiding low antifungal dosage treatments [14]. This study reveals that the mean age of participants was computed to be 31.74±11.77 years. In terms of gender distribution, 78% of all participants were male, and 56% of the entire study cohort fell within the age range of 16-30 years. Notably, 85% of the patients exhibited a disease duration of less than or equal to 12 months. These findings align well with the results of other studies [3-8,10]. For instance, Ramesh etal.1reported a mean participant age of 36.47±11.03 years in their study. Statistically, 64.9% of all participants were female, and 66.7% of the entire study group belonged to the age group of 18-40 years. Additionally, it was observed that 75.4% of the patients had a disease duration of less than or equal to six months.

This study indicates that the most prevalent variant was tineacorporis accounting for 68%, consistent with findings in prior studies [1,15-17]. In a study by Ramesh et al. a similar pattern was observed, with the most common variant being tinea corporis constituting 71.9% in the present study [1].

In this investigation, the aim was to assess the effectiveness and safety of once-daily terbinafine and itraconazole in patients with extensive dermatophytosis. Results revealed a progressive improvement, with 66% of patients showing improvement in the 2-week group, 84% in the 4-week group, and 96% achieving clinical cure in the 6-week group. These outcomes align with previous findings reported by different authors. Majid et al. found an 87% patients are clinically cure from tinea corporis who were treated with terbinafine at 500 mg/day [16]. Similarly, Sanglard D reported 100% cure rates in patients with tinea pedis those who were treated with terbinafine at 250 mg twice daily [17]. Dolton et al. documented that 81.3% patients were clinically cure and a 75% patients were mycologically cure with terbinafine in patients with onychomycosis [18].

This study comes with specific limitations due to its observational nature and survey design, the potential for selection bias cannot be entirely eliminated. Additionally, the study did not account for the use of other antifungal treatments which could have influenced the ultimate outcome. There is a need for long-term comparative studies to address the short comings identified in the present investigation.

Conclusion

This study indicates that the combination of terbinafine with itraconazole results in a higher clinical cure rate. However, neither combination proved effective against tinea infections that had been previously treated with formulations containing topical steroids. There is a pressing need for strict legislation to curb the irrational use of topical corticosteroid-antifungal combination creams. It is crucial to raise awareness among general practitioners about the incorrect use of topical steroid-antifungal preparations. Sensitizing the public to adopt general preventive measures against tinea and ensuring proper treatment for their family members will contribute to reducing the burden of infection.

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