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Original Research Article

Efficacy and Safety of Naftifine 2% Cream versus Terbinafine 1% Cream in Patients with Superficial Fungal Skin Infection: A Randomized Clinical Study

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Abstract

Aim: The aim of the present study was to evaluate the efficacy and safety of naftifine hydrochloride 2% w/w in the patients with dermatophytosis versus terbinafine hydrochloride 1% w/w.

Methods: A retrospective, randomized, two-arm, double-blind, active-controlled, parallel, multicenter, non-inferiority, phase III clinical trial was conducted in the Department of Dermatology and department of Pharmacology, Venereology and Leprosy, Patna Medical College and Hospital, Patna, Bihar, India, for one year. The study involved adult patients diagnosed with superficial fungal infections of tinea cruris and tinea corporis. 60 patients were divided into two study groups based on inclusion and exclusion criteria.

Results: The baseline demographics and characteristics of the disease among these patients were comparable. The test drug showed to be non-inferior to the reference drug for the proportion of patients achieving clinical cure, mycological cure, and composite cure at the end of treatment. The study found that a total of 8 adverse events (AEs) were reported in 10 patients in the group A and 9 in the group B.

Conclusion: The present study concluded that naftifine 2% cream proved to be both effective and safe for Indian patients suffering from dermatophytosis. Further, its efficacy as evaluated by clinical and mycological cure and safety as evaluated by adverse events were found comparable to Terbinafine 1% cream.

Keywords: Dermatophytosis, Naftifine, Terbinafine, Superficial skin fungal infection, Topical antifungals

Introduction

Superficial mycotic infections such as 'Dermatophytosis' is an extremely common infection occurring throughout the world with a reported incidence of 20% in USA. [1] The disease is caused by dermatophytes belonging to genera of Trichophyton, micros Porum and Epidermophyton. The fungal infections of the skin and its appendages are more common in tropical countries like India due to environmental factors like heat (summer) and humidity (monsoon). The risk factors include socio-economic conditions like overcrowding and poverty leading to poor personal hygiene. The type and frequency of dermatophytosis may change with time, due to changes in living standards and application of preventive measures like personal hygiene. However in India, the most commonly occurring clinical type of dermatophytosis for adults includes, tinea corporis (36-59%) and tinea cruris (12-27%). [2,3]

Among these infections, dermatophytosis, commonly known as tinea, stands out as the most prevalent form. This condition arises from dermatophytes found within genera such as Trichophyton, Microspores, and Epidermophyton. Dermatophytes possess a distinctive capability to penetrate the keratin present in skin, hair, and nails to support their proliferation. Among adults, common clinical presentations involve tinea corporis, impacting the trunk and limbs (36-59%), and tinea cruris, affecting the inguinal region (12-27%). Trichophyton rubrum emerges as the primary

causative agent of dermatophytosis in these cases. [4,5]

Desirable attributes of topical treatments for superficial fungal infections encompass broad-spectrum effectiveness, elevated rates of mycological cure, easy-to- follow dosing schedules, minimal adverse reactions, and cost-efficiency. Consequently, ongoing research endeavors aim to develop improved antifungal agents, both topical and systemic, to address these criteria comprehensively. [6] Naftifine emerges as a promising topical antifungal agent, exhibiting broad-spectrum activity against various dermatophytes, as well as other fungal pathogens such as Aspergilla, Sporothrix, and Candida. Available in cream and gel formulations at strengths of 1% and 2%, respectively, naftifine demonstrates fungicidal activity against Trichophyton, micros Porum, and Epidermophyton species in vitro, with minimal inhibitory concentrations ranging from 0.1-0.2 mg/ml. [7-11] Notably, its efficacy extends beyond antifungal properties to include significant antibacterial and anti-inflammatory effects. [10]

The aim of the present study was to evaluate the efficacy and safety of naftifine hydrochloride 2% w/w in the patients with dermatophytosis versus terbinafine hydrochloride 1% w/w.

Materials and Methods

A retrospective randomized, two-arm, double-blind, active-controlled, parallel, multicenter, non-inferiority, phase III clinical trial was conducted in the Department of Dermatology and Department of Pharmacology, Venereology and Leprosy, Patna Medical College and Hospital, Patna, Bihar, India for one year. The study involved adult patients diagnosed with superficial fungal infections of tinea cruris and tinea corporis. 60 patients were divided into two study groups based on inclusion and exclusion criteria.

Group A: 2% Naftifine

Group B: 1% Terbinafine

Study Subjects

The inclusion criteria included age range (18-65), acute symptomatic tinea corporis or tinea cruris, limited involvement, mycological diagnosis confirmed by microscopic KOH test, and a total clinical score of at least 5. Patients were required to provide written informed consent and comply with protocol requirements.

Patients were disqualified from the study if they had a known hypersensitivity to naftifine or terbinafine, suffered from extensive or disseminated tinea infections, exhibited skin lesions complicated by secondary bacterial infections, presented with other dermatological conditions that could confound disease assessment and treatment evaluation, had uncontrolled systemic diseases of clinical significance, suffered from immune- suppressive disorders, experienced hepatic or renal dysfunction, used topical antifungal agents within 30 days before enrollment, were pregnant or lactating females, or were female patients of childbearing potential unwilling to use effective contraception. Additionally, patients with a history of alcohol and/or drug abuse, those who had participated in another clinical trial within the past 3 months before screening, or individuals for whom the investigator deemed participation inappropriate were excluded from the study.

Dosing Regimen

The study drugs were applied as a thin layer over the affected skin areas and immediate surrounding (approx. 1 inch) healthy skin once daily for 2 weeks. Patients were instructed to clean and dry the affected area(s) before each application and to leave the treated area(s) uncovered for at least 10 minutes after each application. Patients were also instructed to maintain a daily record of usage of the study drug in their dosing cards.

Study Conduct

The patients were screened at the first visit, followed by a general and systemic examination. Laboratory investigations, skin scrapings, and total clinical scores were recorded. Eligible patients were randomized to study arms, and the study drug was dispensed according to the randomization number. A dosing card was given to record daily usage. Patients were followed up after one week for adverse events, and unused drugs were collected for compliance evaluation. The TCS was determined through the evaluation of clinical symptoms and skin scrapings. After the treatment, similar assessments were conducted after an additional week, and overall tolerability was evaluated. Patients who attained clinical or mycological cure were monitored for an additional two weeks to assess for any signs of relapse.

Study Endpoints

The patients were assessed for efficacy & safety. The primary endpoint was defined as a clinical cure at the end of the treatment when the patient's TCS was ≤ 2 with no itching (score 0) and an individual score of erythema and scaling should also be 1 or 0 at the follow-up and end of treatment. The secondary endpoints included mycological cure, composite cure, and global assessment of efficacy at the end of the treatment. The clinical and mycological relapses were evaluated during the post-treatment follow- up.

The study assessed clinical signs and symptoms on a 4- point scale, ranging from grade 0 i.e. no signs & symptoms to 3 i.e. severe. The total score was

considered TCS. Mycological cure was assessed using skin scraping for microscopic KOH to detect fungal hyphae. Patients with both clinical and mycological cures at the end of treatment were considered composite cures. Patients with both at the end of treatment but with clinical signs or symptoms at the treated area or positive KOH test were considered clinical relapse or mycological relapse.

The global assessment of efficacy was assessed by the investigator during visit 4 on a 6-point scale.16 Safety was assessed by recording AEs throughout the study, including hematological and biochemical laboratory investigations. All abnormalities in physical examinations and clinically significant laboratory findings were recorded as AEs. AEs were observed or volunteered, regardless of the study group or drug causal relationship. The investigator rated the overall tolerability of the study treatment at visit 4 on a 4-point scale such as excellent, good, fair, or poor. The AEs considered related to the study drug only were considered for tolerability grading by the investigator.

Statistical Analysis

The sample size for the primary endpoint was calculated on the basis that at least 240 subjects (Test: 120, Reference: 120) will be required to achieve the non- inferiority of the test drug as compared to the reference drug at 90% power and 2.5% one-sided level of significance, assuming that at least 85% patients will achieve clinical cure at the end of the treatment with no difference between the test group and the reference group, and considering the non-inferiority margin of - 15%.

Results

Table 1: Demographic data

Parameters		Group A (n=30)	Group B (n=30)	P value
Age (years) (mean± SD)		37.6±11.5	38.9±10.6	0.32
Gender, frequency (%)	Male	18	17	
	Female	12	13	0.08
Height (cm) (mean± SD)		165.0±7.6	164.4±7.0	0.46
Weight (kg) (mean± SD)		65.0±8.6	64.9±8.4	0.91
Body mass index (kg/m^2) (mean± SD)		23.9±2.1	24.0±2.4	0.62
SBP (mmHg) (mean± SD)		121.4±4.8	122.0±4.7	0.34
DBP (mmHg) (mean± SD)		78.6±4.5	78.5±4.0	0.86
Respiratory rate (/min) (mean± SD)		17.8±1.3	17.6±1.3	0.28
Pulse Rate (/min) (mean± SD)		77.7±4.1	77.8±4.3	0.81
Temperature (°F) (mean± SD)		98.0±0.6	98.1±0.5	0.40
Type of *Tinea* infection, frequency	*Tinea corporis*	21	18	
(%)	*Tinea cruris*	9	12	0.38
No. of skin lesions (mean± SD)		2.4±1.1	2.3±1.0	0.48
Greatest surface diameter (cm) (mean± SD)		3.3±1.0	3.3±1.0	0.92
	Erythema	2.3±0.8	2.4±0.7	0.47
Clinical score (mean± SD)	Scaling	2.1±0.6	2.0±0.7	0.46
	Itching	2.2±0.6	2.3±0.6	0.65

The baseline demographics and characteristics of the disease among these patients were comparable.

Table 2: Proportion of the patients with clinical cure, mycological & composite cure

Group A (n=30)	Group B (n=30)	P value
Primary endpoint: patients achieving clinical cure at the end of treatment, N		
28	26	0.08
Patients achieving mycological cure at the end of treatment, N (%)		
28	27	0.26
Patient achieving composite cure at the end of treatment, N (%)		
28	27	0.08

The test drug showed to be non-inferior to the reference drug for the proportion of patients achieving clinical cure, mycological cure, and composite cure at the end of treatment.

Table 3: Summary of adverse events

Adverse events, frequency (%)	Group A (n=30)	Group B (n=30)	P value
Local/application site	1	2	0.57
Burning	1	1	1.0
Dryness	1	2	0.37
Irritation	1	1	0.62
Itching	1	1	1.0
Systemic	1	1	1.0
Headache	1	1	1.0
Fever	1	-	1.0
Vomiting	-	1	0.50

The study found that a total of 8 adverse events (AEs) were reported in 10 patients in the group A and 9 in the group B.

Discussion

In clinical settings around the globe, superficial fungal infections are a common issue. The world health organization (WHO) estimates that its prevalence is between 20 and 25% worldwide and that it has been steadily increasing over time. [12,13] This tendency is especially noticeable in tropical and subtropical areas, such as India, where the extreme humidity and heat promote the growth of fungi. Poverty and overcrowding are factors that heighten the risk and often result in inadequate personal hygiene practices. [13,14] While superficial fungal infections typically aren't life- threatening, they can induce severe symptoms and greatly diminish the quality of life. [15]

The baseline demographics and characteristics of the disease among these patients were comparable. The test drug showed to be non-inferior to the reference drug for the proportion of patients achieving clinical cure, mycological cure, and composite cure at the end of treatment. The study found that a total of 8 adverse events (AEs) were reported in 10 patients in the group A and 9 in the group B. Dermatophytosis, a common fungal infection caused by keratophakic fungi known as dermatophytes, presents significant management challenges. [16,17] These include an increase in chronic and recurrent cases, genetic mutations enhancing fungal persistence, and the rapid emergence of drug-resistant species due to inadequate antifungal doses. Moreover, there is a shift in causative organisms from Trichophyton rubrum to Trichophyton mentagrophytes, which have a rapid replication rate, longer survival time, and higher inhibitory concentrations, complicating effective management. [16,18]

One of the primary challenges stems from the improper use of commonly used topical imidazole antifungals. Patients often discontinue treatment upon observing the disappearance of infection symptoms, leading to the emergence of drug-resistant organisms. [19] Due to this technique, azole resistance in dermatophytes has become more common; in certain parts of the world, this incidence has been observed to reach 19%. The fungus may go latent and produce spores, only to reappear when therapy is stopped. This can result in recurrence and persistent tinea infections, which can cause patients great misery on a social, emotional, and economic level. [20]

Conclusion

The present study concluded that naftifine 2% cream proved to be both effective and safe for Indian patients suffering from dermatophytosis. Further, its efficacy as evaluated by clinical and mycological cure and safety as evaluated by adverse events were found comparable to Terbinafine 1% cream.

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