

Original Research Article

A phase III randomized controlled clinical trial evaluating the efficacy and safety of naftifine 2% cream versus terbinafine 1% cream in patients with superficial fungal infection of the skin

Nibedita Patro¹, Prerna R. Suryatale², Ipsa Pandya³, Nadia Zakir Mian⁴, Monika Chinda^{5*}, Pavankumar M. Daultani⁶, Ravindra Mittal⁶, Ashok D. Jaiswal⁵, Anit Singh⁷

¹Department of Skin and VD, Hi-Tech Medical College and Hospital, Pandara, Bhubaneswar, Odisha, India

²Department of Dermatology, Jeevan Rekha Hospital, Belagavi, Karnataka, India

³Department of Dermatology, Aatman Hospital, Bopal, Ahmedabad, Gujarat, India

⁴Department of Dermatology, Prakhar Hospital Pvt. Ltd, Kanpur, Uttar Pradesh, India

⁵Department of Medical Affairs, Zydus Healthcare Ltd., Mumbai, Maharashtra, India

⁶Department of New Product Development, Zydus Healthcare Limited, Ahmedabad, Gujarat, India

⁷Clinical Research Network India, Delhi, India

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***Correspondence:**

Dr. Monika Chinda,

E-mail: monika.chinda@zyduslife.com

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ABSTRACT

Background: Dermatophytosis is the prevailing fungal infection, typically addressed through topical, systemic antifungal medications, or a combination of both. Naftifine hydrochloride, belonging to the allylamine group, is a topical antifungal, exhibiting fungicidal properties alongside antibacterial and anti-inflammatory effects. This study evaluated the efficacy and safety of naftifine hydrochloride 2% w/w in 268 patients with dermatophytosis versus terbinafine hydrochloride 1% w/w.

Methods: The drugs were applied daily for two weeks, with the primary endpoint being a clinical cure at the end of the treatment. Secondary endpoints included mycological cure, composite cure, global efficacy assessment, and post-treatment relapse.

Results: In both groups, most patients experienced both clinical and mycological cures, with composite cures observed in 94.07% of the test group and 87.97% of the reference group. The global assessment of efficacy was 3.59 in the test group and 3.48 in the reference group, showing no notable difference between the two groups. All adverse events in both groups were mild and resolved within four days. Overall tolerability was comparable between the study groups.

Conclusions: The study concluded that topical naftifine was effective and safe in patients with dermatophytosis and its efficacy and safety were found comparable to topical terbinafine.

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

INTRODUCTION

In clinical settings around the globe, superficial fungal infections are a common issue. The world health

organisation (WHO) estimates that its prevalence is between 20 and 25% worldwide and that it has been steadily increasing over time.^{1,2} 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.^{2,3} While superficial fungal infections typically aren't life-threatening, they can induce severe symptoms and greatly diminish the quality of life.⁴

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*, *Microsporum*, 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.^{5,6} Treatment of dermatophytosis typically involves the use of topical or systemic antifungal agents, selected based on factors such as severity, infection site, and causative organism. Topical antifungals, owing to their efficacy and favorable safety profile, often constitute the first-line treatment for uncomplicated tinea infections. They penetrate the skin surface, exerting fungicidal or fungistatic effects and facilitating clinical and mycological resolution.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 endeavours aim to develop improved antifungal agents, both topical and systemic, to address these criteria comprehensively.⁷ 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*, *Microsporum*, and *Epidermophyton* species *in vitro*, with minimal inhibitory concentrations ranging from 0.1-0.2 mg/ml.⁸⁻¹² Notably, its efficacy extends beyond antifungal properties to include significant antibacterial and anti-inflammatory effects.¹¹

Mechanistically, naftifine specifically targets the fungal enzyme squalene epoxidase, which plays a crucial role in the ergosterol biosynthesis pathway necessary for maintaining fungal cell membrane integrity. Although squalene epoxidase is also implicated in mammalian cholesterol production, naftifine demonstrates a high degree of selectivity for fungal enzymes, leading to minimal interference with mammalian cholesterol synthesis.¹¹ Clinical studies evaluating naftifine hydrochloride formulations have demonstrated superior efficacy compared to placebo in achieving both clinical

and mycological cures in patients with tinea corporis, cruris, and pedis.^{8,13-15} Additionally, comparative studies with other topical antifungals, including clotrimazole, econazole, miconazole, and terbinafine, have established naftifine's comparable efficacy and safety profiles, reinforcing its position as a valuable therapeutic option for dermatophytosis.¹² Recently, the first formulation of naftifine 2% cream was introduced in India for the treatment of superficial fungal infection of the skin by M/s. Zydus Healthcare Ltd. The current phase III clinical trial aims to assess the antifungal efficacy and safety profile of a naftifine hydrochloride 2% w/w cream in patients with dermatophytosis (tinea cruris and tinea corporis) compared to a topical terbinafine hydrochloride cream at 1% w/w.

METHODS

Study design

A prospective, randomized, two-arm, double-blind, active-controlled, parallel, multicenter, non-inferiority, phase III clinical trial from April 2022 to June 2022. This study was conducted in accordance with 'New Drugs and Clinical Trials Rules 2019 and Indian good clinical practices guidelines. All participants provided written informed consent prior to enrollment.

Study subjects

The study involved adult patients diagnosed with superficial fungal infections of tinea cruris and tinea corporis. Eligible patients were divided into two study groups based on inclusion and exclusion criteria. 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 (Table 1).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 (Table 2). The AEs considered related to the study drug only were considered for tolerability grading by the investigator.

Table 1: Global assessment of efficacy score at the end of treatment.

Score	Criteria
-1	Exacerbation (flare-up at the site of treatment)
0	Unchanged
1	Mild improvement (<50% clearance)
2	Moderate improvement (50% to 75% clearance)
3	Excellent improvement (75% to 100% clearance)
4	Cleared (100% clearance)

Table 2: 4-point tolerability scale.

Tolerability grade	Criteria
Excellent	No adverse event reported
Good	Mild adverse events reported which subsided with or without medication and did not necessitate stoppage of study drug
Fair	Moderate adverse events reported which subsided with or without medication and did not necessitate stoppage of study drug
Poor	Severe or serious adverse events, or adverse events which necessitated stoppage of study drug

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%.¹⁷⁻¹⁹ Thus, considering the drop-out rate of around 10%, 268 patients were enrolled in the study with 1:1 allocation ratio.

For the analysis of effectiveness, both Per Protocol (PP) and modified Intention to Treat (mITT) analyses were scheduled. The PP population consisted of all randomized subjects who had completed the specified post-randomization visit according to the protocol, including those with minor protocol deviations. The mITT population comprised subjects who had completed the post-randomization visit, even if they had major protocol deviations.

The PP analysis was designated as the primary analysis, with the mITT analysis serving as supportive. In terms of safety, all randomized subjects who had taken at least one dose of the study drug were included in the safety analysis.

RESULTS

A group of 268 patients diagnosed with dermatophytosis underwent assessment for both efficacy and safety. Table 3 outlines the baseline demographics and characteristics of the disease among these patients.

Assessment of efficacy

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 as shown in (Table 4). The mean TCS at the screening visit was 6.59 and 6.63 in the test group and the reference group respectively. In the test group, the mean TCS reported at the 1-week follow-up after treatment and at the end of treatment was 3.29 and 0.80 respectively. Likewise, in the reference group, the mean TCS reported at the 1-week follow-up after treatment and at the end of treatment was 3.40 and 1.03 respectively.

Table 3: Baseline demographics of patients with dermatophytosis.

Parameters	Test group (n=135)	Reference group n=133)	P value	
Age (years) (mean±SD)	37.6±11.5	38.9±10.6	0.32	
Gender, frequency (%)	Male	80 (59.3)	81 (60.9)	0.08
	Female	55 (40.7)	52 (39.1)	
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	98 (72.6)	90 (67.7)	0.38
	Tinea cruris	37 (27.4)	43 (32.3)	
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	
Clinical score (mean±SD)	Erythema	2.3±0.8	2.4±0.7	0.47
	Scaling	2.1±0.6	2.0±0.7	0.46
	Itching	2.2±0.6	2.3±0.6	0.65

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, *Data presented as mean±SD, #Data presented as N (%).

Table 4: Proportion of the patients with clinical cure, mycological & composite cure.

Test group (n=135)	Reference group (n=133)	Diff. T-R (95% CI)	P value
Primary endpoint: patients achieving clinical cure at the end of treatment, N (%)			
127 (94.1)	117 (88.0)	6.1 (-1.4 to 13.8)	0.08
Patients achieving mycological cure at the end of treatment, N (%)			
130 (96.3)	124 (93.2)	3.1 (-3.1 to 9.6)	0.26
Patient achieving composite cure at the end of treatment, N (%)			
127 (94.07)	117 (87.97)	6.10 (-1.41 to 13.83)	0.08

P value by Chi Square test; test group vs. reference group.

There was a statistically significant fall in TCS in both study groups at 1-week follow-up after treatment and at the end of treatment as compared to the screening visit (p<0.00001). Further, the mean TCS including the mean scores of clinical signs and symptoms were comparable between the study groups at the baseline and during the treatment period (p>0.05) (Figure 1). The test study group had a mean global assessment of efficacy score of 3.59, while the reference group had a score of 3.48 (p=0.24). No patient experienced a clinical or

mycological relapse, while one patient in the reference group experienced a clinical relapse. The difference in clinical relapse rates was not statistically significant (p=0.50).

Assessment of safety

The study found that a total of 7 adverse events (AEs) were reported in 7 patients in the test group and 9 in the reference group (Table 5), with all AEs being mild and resolved within 4 days, with no serious adverse event

reported in any patient. In the test group, 94.8% of patients were given an ‘excellent’ grade, and 5.2% of patients were given a ‘good’ grade while in the reference group, 93.3% of patients were given an ‘excellent’ grade and the remaining 6.7% patient was given a ‘good’ grade

of tolerability. None of the patients in both groups was given a fair or poor grade of tolerability. The overall tolerability evaluation was comparable between the study groups (p=0.58).

Table 5: Summary of adverse events.

Adverse events, frequency (%)	Test group, (n=135)	Reference group, (n=133)	P value
Local/application site	5 (3.7)	7 (5.3)	0.57
Burning	2 (1.5)	1 (0.8)	1.0
Dryness	1 (0.7)	3 (2.3)	0.37
Irritation	1 (0.7)	2 (1.5)	0.62
Itching	1 (0.7)	1 (0.8)	1.0
Systemic	2 (1.5)	2 (1.5)	1.0
Headache	1 (0.7)	1 (0.8)	1.0
Fever	1 (0.7)	-	1.0
Vomiting	-	1 (0.8)	0.50

Data presented as N (%); *Fisher’s exact test (test group vs. reference group).

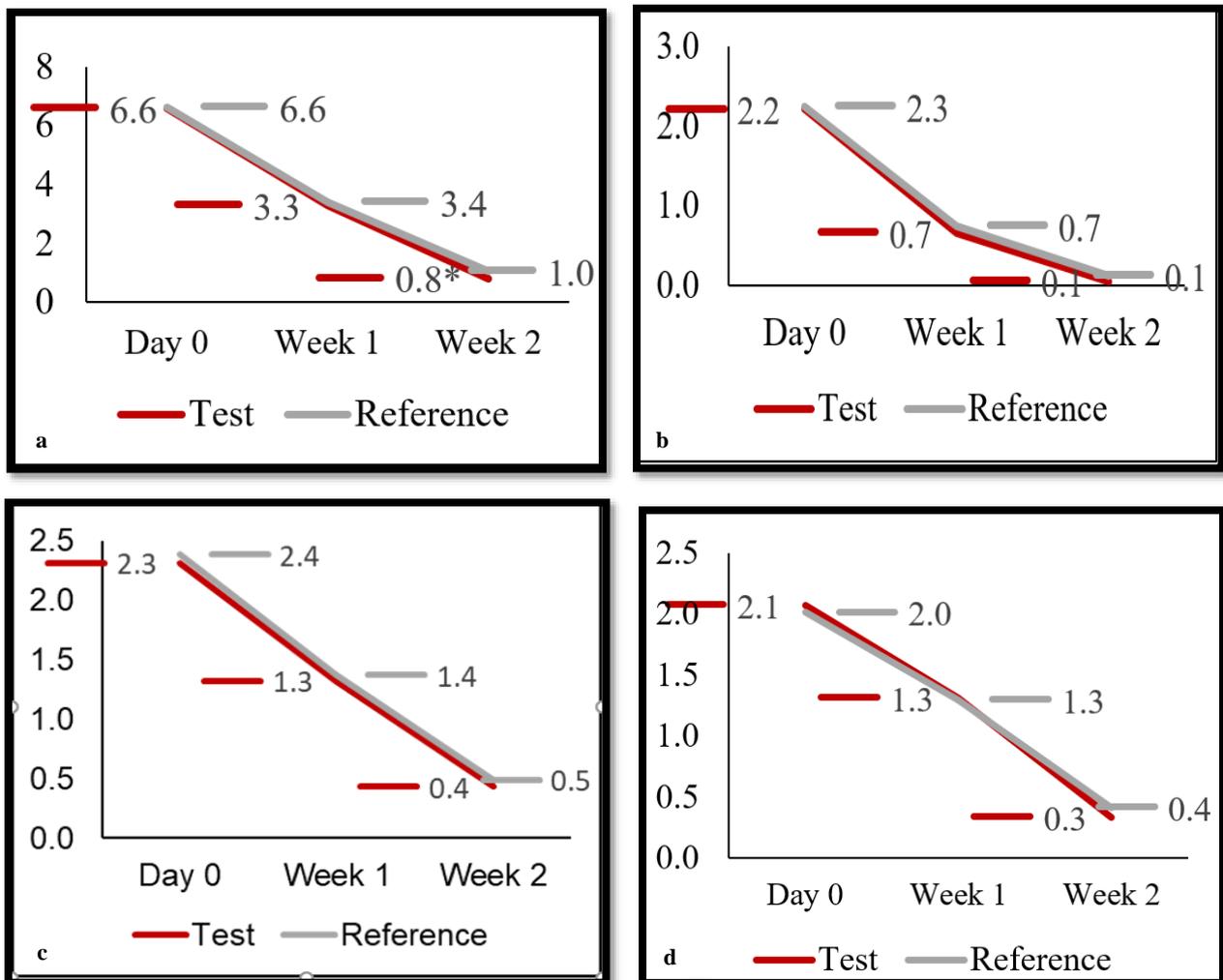


Figure 1: Clinical score at the screening and during the treatment period, a) total clinical score, b) itching score, c) erythema score, d) scaling score.

DISCUSSION

Dermatophytosis, a common fungal infection caused by keratinophilic fungi known as dermatophytes, presents significant management challenges.^{20,21} 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.^{20,22}

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.²³ 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.²⁴

Another significant challenge lies in the prolonged duration of treatment required for dermatophytosis, which can span weeks to months, often considered expensive and time-consuming. There is thus a critical need for antifungal agents with shorter treatment durations to improve patient quality of life and mitigate the emergence of drug-resistant strains due to prolonged management.²⁴

Naftifine, a synthetic allylamine antifungal, presents a promising solution. Because of its strong lipophilicity, it may penetrate the stratum corneum and hair follicles with efficiency and at high concentrations. Higher effectiveness rates are provided by allylamines such as naftifine, which have a fungicidal action, gradual release from the stratum corneum, and maybe stronger keratin binding than imidazoles. The promise of naftifine 2% cream as a therapy option for individuals with dermatophytosis is further highlighted by its once-daily administration.²³ Clinical research backs up the effectiveness of naftifine in treating patients with tinea corporis and tinea cruris when compared to placebo, demonstrating improved mycological and clinical cure rates at 4 weeks and 21 days, respectively. Furthermore, naftifine has shown therapeutic success in the US and Europe against a variety of dermatomycoses.

In studies comparing naftifine with econazole and clotrimazole for the treatment of tinea cruris, tinea corporis, tinea pedis, and candidiasis, similar efficacy was observed, with naftifine showing a faster onset of action.²⁵ The research investigates the efficacy and safety of naftifine 2% cream versus terbinafine 1% cream in the

treatment of dermatophytosis among Indian patients. Naftifine 2% cream showed non-inferior results for a clinical cure and secondary endpoints.

Safety was comparable between study groups, with no clinically significant abnormalities reported. Both arms showed comparable evaluations in terms of overall tolerability, with no clinically significant abnormalities reported in hematological and biochemical laboratory investigations.

Limitations

The study had certain limitations such as limited post-treatment follow-up. The patients included in the study had symptomatic tinea infection in a single body region with limited involvement.

CONCLUSION

The findings from this double-blind clinical trial, which was randomized and active-controlled, indicate 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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Conflict of interest: None declared

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

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