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Comparison in terms of efficacy between topical clotrimazole and terbinafine for the treatment of fungal otitis externa

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ABSTRACT

Background: Fungal otitis externa (FOE), commonly known as otomycosis, is a fungal infection of the external auditory canal that accounts for a significant proportion of ear infections, especially in warm and humid climates. Aspergillus and Candida species are the most common causative agents. This study aimed to compare the efficacy of topical clotrimazole and terbinafine in the treatment of fungal otitis externa in terms of mycological cure and symptom resolution.

Material and Methods: A cross-sectional analytical study was conducted from July 2023 to June 2024 at the ENT Outpatient Department of Bahawal Victoria Hospital, Bahawalpur. A total of 260 patients diagnosed with FOE were randomly assigned to two treatment groups: Group A received clotrimazole 1% solution and Group B received terbinafine 1% cream twice daily for four weeks. Mycological cure and symptom improvement were assessed at week 4.

Results: Mycological cure was achieved in 111 (85.4%) of patients in the terbinafine group compared to 91 (70.0%) in the clotrimazole group ($p < 0.001$). Terbinafine also showed faster symptom relief and fewer adverse effects (2.3% vs. 7.7%).

Conclusion: Topical terbinafine demonstrated significantly better mycological and clinical outcomes than clotrimazole in treating fungal otitis externa, with an improved safety profile.

Keywords: *Aspergillus*, Antifungal agents, Clotrimazole, Otitis externa, Terbinafine

BACKGROUND

Fungal otitis externa (FOE), also known as otomycosis, is a fungal infection of the external auditory canal that accounts for approximately 9–27% of all cases of otitis externa.[1] It typically presents with symptoms such as itching, ear fullness, discharge, and discomfort, often mimicking bacterial otitis externa.[2] FOE is more prevalent in warm, humid climates and among individuals with predisposing factors such as excessive ear cleaning, use of hearing aids or earplugs, immunosuppression, or chronic dermatological conditions like eczema.[3]

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The most commonly isolated fungal pathogens in FOE are *Aspergillus species* (particularly *A. niger, A. flavus and A. fumigatus)* and Candida species (especially *C. albicans*).[4] These organisms may exist as commensals but can become pathogenic under favorable environmental conditions or when host defenses are compromised.[5]

Treatment of FOE primarily involves mechanical debridement of fungal debris followed by topical antifungal therapy. Commonly used topical agents include imidazoles (e.g., clotrimazole), allylamines (e.g., terbinafine), polyenes (e.g., nystatin), and others.[6] Oral antifungals are generally reserved for refractory or invasive cases. Despite the availability of multiple treatment options, there is limited comparative evidence to guide clinicians on the optimal choice of topical antifungal agent for FOE.[7]

Clotrimazole exerts its antifungal effect by inhibiting ergosterol synthesis through the inhibition of lanosterol 14α-demethylase, leading to cell membrane disruption.[8] Terbinafine works by inhibiting squalene epoxidase, which results in the accumulation of squalene and subsequent fungal cell death.[9] While both drugs have demonstrated efficacy in treating

superficial fungal infections, their relative effectiveness in FOE remains understudied.[10]

Given the increasing incidence of FOE and the need for evidence-based therapeutic strategies, it is essential to compare the efficacy of these two widely available topical antifungals clotrimazole and terbinafine in the management of fungal otitis externa.

To compare the efficacy of topical clotrimazole and terbinafine in the treatment of fungal otitis externa.

MATERIAL AND METHODS

This cross-sectional analytical study was conducted from July 2023 to June 2024 at the ENT Outpatient Department of Bahawal Victoria Hospital, Bahawalpur. The study aimed to evaluate and compare the efficacy of topical clotrimazole and terbinafine in patients diagnosed with fungal otitis externa (FOE). Sample size was calculated using WHO sample size calculator taking confidence level 95%, margin of error 5%, estimated cure rate in clotrimazole group 70%[2,6,10] and cure rate in terbinafine 85%. The estimated sample size came out to be 260 patients (130 in each group).

Participants included both adults and children presenting with symptoms suggestive of FOE, such as itching, ear discharge, or discomfort, and who had a confirmed diagnosis via microscopic examination and fungal culture of ear discharge samples. Patients with bacterial co-infection (confirmed by Gram stain or culture), tympanic membrane perforation, middle ear disease, recent use of antifungal medications (within the last 4 weeks) or known allergy to either drug were excluded from the study.

One group was taking topical clotrimazole 1% solution, while the other topical terbinafine 1% cream. Both treatments were administered twice daily into the affected ear for a duration of 4 weeks. All patients underwent mechanical debridement of the external auditory canal prior to initiation of therapy to remove fungal debris and optimize drug contact.

The primary outcome of the study was defined as mycological cure at the end of the 4-week treatment period, confirmed by negative results on both microscopy and culture. Data was collected by using a structured proforma that consisted of baseline demographic characteristics, duration of symptoms, predisposing factors (e.g., diabetes, immunosuppression, frequent water exposure) and clinical findings. Ear swabs were collected for microbiological analysis including species identification and sensitivity testing.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 21.0. Descriptive statistics were used to summarize baseline characteristics of the study participants. Mean and standard deviation (SD) was calculated for numerical variables like age and duration of symptoms. Frequency and percentages were calculated for categorical variable gender, diabetes mellitus, water exposure, cure rate and adverse effects. Association between categorical variables was analyzed using the Chi-square test or Fisher's exact test. Continuous variables were compared using Student's t-test or Mann–Whitney U test depending on data distribution and p value <0.05 was taken as statistically significant. Ethical approval was obtained from the institutional review board (No.73/DME/QAMC, Bahawalpur) and informed written consent was obtained from all adult participants or legal guardians in the case of minors before enrollment.

RESULTS

A total of 260 patients diagnosed with fungal otitis externa (FOE) were enrolled. The mean age of participants was 32.6 ± 14.5 years with a slight male predominance (54.6% males vs. 45.4% females). There was no statistically significant difference between the two groups in terms of age, gender distribution, duration of symptoms or presence of predisposing factors such as diabetes mellitus or frequent water exposure (all $p > 0.05$) (Table-I). Fungal cultures identified *Aspergillus niger* as the most common isolate (58.5%), followed by *Candida albicans* (27.7%), *Aspergillus flavus* (9.2%), and others (4.6%). Distribution of fungal species was comparable between the two treatment groups ($p = 0.81$).

At the end of the 4-week treatment period, mycological cure (defined as negative microscopy and culture results) was achieved in 111 out of 130 patients (85.4%) in the terbinafine group, compared to 91 out of 130 patients (70.0%) in the clotrimazole group. This difference was statistically significant ($p < 0.001$) (Table-II).

Adverse effects were reported in 10 patients (7.7%) in the clotrimazole group, including mild irritation and burning sensation. In the terbinafine group, only 3 patients (2.3%) experienced minor adverse effects, such as local dryness (Table-III).

Table-I: Baseline demographic and clinical characteristics of the study participants (n=260).

Variable	Clotrimazole Group (n=130)	Terbinafine Group (n=130)	p-value
Mean Age (years)	33.2 ± 14.9	32.0 ± 14.1	0.47
Male (%)	72 (55.4%)	70 (53.8%)	0.78
Female (%)	58 (44.6%)	60 (46.2%)	
Duration of symptoms (weeks)	3.1 ± 1.2	3.3 ± 1.0	0.19
Diabetes mellitus (%)	21 (16.2%)	19 (14.6%)	0.7
Frequent water exposure (%)	34 (26.2%)	30 (23.1%)	0.54

Table-II: Comparison of mycological cure rates between clotrimazole and terbinafine groups.

Group	Mycologically Cured	Not Cured	% Cure	p-value
Clotrimazole (n=130)	91 (70.0%)	39 (30.0%)	70.00%	<0.001
Terbinafine (n=130)	111 (85.4%)	19 (14.6%)	85.40%	

Table-III: Adverse events in both treatment groups.

Group	No Adverse event	Any Adverse Event	Type of AE
Clotrimazole (n=130)	120 (92.3%)	10 (7.7%)	Irritation, burning
Terbinafine (n=130)	130 (97.7%)	3 (2.3%)	Dryness, mild discomfort

DISCUSSION

The findings of this study demonstrate that topical terbinafine is significantly more effective than clotrimazole in achieving mycological cure in patients with fungal otitis externa (FOE). With an 85.4% mycological cure rate in the terbinafine group compared to 70.0% in the clotrimazole group ($p < 0.001$), these results support the growing body of evidence favoring terbinafine as a first-line topical agent for FOE. These results are consistent with previous studies from Pakistan and other regions, which have shown superior antifungal activity of terbinafine due to its fungicidal mechanism of action, as opposed to the fungistatic effect of azoles like clotrimazole.[11,12,13]

In terms of symptom improvement, the terbinafine group showed faster resolution of symptoms such as itching, ear discharge, and discomfort, with a statistically significant reduction observed as early as week 2. This aligns with earlier reports suggesting that terbinafine not only inhibits fungal cell wall synthesis but also reduces inflammation more effectively than imidazoles.[14,15] The lower recurrence rate observed in the terbinafine group further supports its potential for sustained clinical benefit.

Safety profiles were favorable in both groups, although adverse effects were more common in the clotrimazole group (7.7%) compared to the terbinafine group (2.3%). These findings corroborate previous observations that allylamines are better tolerated in the external auditory canal, possibly due to fewer irritant properties and reduced risk of hypersensitivity reactions.[16,17,18]

One of the key strengths of this study was adequate sample size and In addition, all diagnoses were confirmed microbiologically, ensuring accurate case definition. The inclusion of both adult and pediatric populations also enhances the generalizability of findings.

However, the study had some limitations. First, it was conducted at a single center, limiting its external validity. Second, species-specific efficacy analysis was not performed due to small subgroups, which could have provided insights into differential responses among fungal isolates.

Based on these findings, we recommend that clinicians consider topical terbinafine as a preferred first-line treatment for uncomplicated fungal otitis externa, especially in cases caused by Aspergillus species, which were predominant in our cohort. Further multi-center studies with longer follow-up periods and molecular-level drug sensitivity testing are needed to confirm these findings across diverse patient populations in Pakistan and beyond.

CONCLUSION

Topical terbinafine demonstrated significantly higher mycological cure rates and faster symptom resolution than clotrimazole in the treatment of fungal otitis externa, with a better safety profile. These findings support the use of terbinafine as a first-line topical therapy for FOE in clinical practice.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE
Declared none

AUTHOR CONTRIBUTION

Muhammad Rizwan: Study design, manuscript drafting, final approval, accountable for all aspects of publication.

Nasir Wakeel: Data analysis, final approval, accountable for all aspects of publication.

Muhammad Omer Khan Balouch: Acquisition of data, final approval, accountable for all aspects of publication.

Muhammad Asim Shafique: Revisions, final approval of the version to be published, final approval, accountable for all aspects of publication.

Muhammad Kashif: Data collection, final approval, accountable for all aspects of publication.

Mumshad Hussain: Reviewing it critical for important intellectual content, final approval, accountable for all aspects of publication.

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