

Comparison of Efficacy of Terbinafine 1% Lotion and Cream Versus Clotrimazole 1% Solution and Cream in Otitomycosis

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ABSTRACT

Objective: To compare the efficacy of terbinafine 1% lotion and cream versus clotrimazole 1% solution and cream in otomycosis.

Study design: Quasi-experimental study.

Place and Duration of the study: ENT Department, Combined Military Hospital Multan, Pakistan from Apr to Dec 2023.

Methodology: A total of 66 cases of otomycosis were included. They were divided into Group-A (1% Terbinafine) and Group-B (1% Clotrimazole) based on laterality of the infection. Efficacy was analyzed in terms of achievement of complete cure and compared between the two groups.

Results: Median age was 39.00 (57.00 – 19.00) years. There were 24(36.36%) male and 42(63.64%) female patients. Median BMI was 29.85 (37.50 – 19.60) kg/m². There were 35(53.03%) patients who had diabetes, 7(10.61%) had hypertension and 7(10.61%) were smokers. Most common presenting symptom among patients diagnosed with otomycosis was ear itching 44(66.67%). Median pretreatment composite symptoms score was 3.00 (10.00 – 1.00). In Group-A (n=33), frequency of complete cure was 27 (81.82%), while in Group-B (n=33), it was 16 (48.48%); ($p=0.004$).

Conclusion: Terbinafine is significantly more efficacious as compared to clotrimazole in treatment of otomycosis.

Keywords: Clotrimazole, Dermatophytosis, External Ear Canal, Terbinafine.

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INTRODUCTION

Dermatophytes are the leading cause of fungal infections (dermatophytosis) in the world, with a global prevalence of 20-25%.¹ In Pakistan, according to a recent study, among various skin samples examined in a sub-set of population, prevalence of dermatophytes infection was 31.29%.² These fungi have exhibited an increase in resistance towards various anti-fungal agents.^{3,4} There are numerous host defensive mechanisms that prevent the spread of infection, including skin type, UV exposure, dryness and warm temperature.⁵ However, when the infection ensues, it becomes very difficult to treat due to its resistant and relapsing nature for which various anti-fungals in different formulations as monotherapy or in the form of combination are used.⁶

Otitomycosis is the fungal infection of the external ear canal which is caused by several different fungi.⁷ Since fungal infections are more common in hot and humid environments, otomycosis is much more

prevalent in individuals, residents of tropical regions, those who frequently swim in the pools and do not practice drying their external ear canal and patients who are immunocompromised like diabetic patients.^{8,9}

When it comes to treatment of otomycosis, multiple anti-fungal medications and antiseptic solutions are used including the povidone-iodine, terbinafine, voriconazole, clotrimazole, boric acid, amphotericin-B, posaconazole, miconazole, fluconazole, caspofungin and terbinafine.¹⁰ However, when it comes to comparison of efficacy of terbinafine 1% lotion and cream versus clotrimazole 1% solution and cream in otomycosis, no head-to-head comparison at regional as well as international level was found despite extensive literature search. Therefore, to fill this research gap, the present study was conducted with the aim to compare the efficacy of terbinafine 1% lotion and cream versus clotrimazole 1% solution and cream in otomycosis.

METHODOLOGY

This quasi-experimental study was conducted at Combined Military Hospital, Multan, Pakistan from April 2023 to October 2023, after getting approval

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from the Institutional Ethical Review Board (Ref No: ERC 53/2022, dated 6/10/2022).

Inclusion Criteria: Adult patients of either gender, aged 18 years or above who were diagnosed with culture-proven otomycosis by the fungi sensitive to terbinafine and clotrimazole were included.

Exclusion Criteria: Patients with coexistent bacterial infection of the ear, bilateral infection, patients taking anti-fungal therapy due to other fungal infection, those who were allergic to either study drug, pregnant women, lactating mothers and those with structural disease of the ear were excluded.

For sample size calculation, anticipated efficacy of terbinafine and clotrimazole were taken at 76% and 37.5%, respectively.¹¹ This gave a sample size of 66 (33 in each group), which was selected using non-probability consecutive sampling.

Before inclusion, informed written consent was obtained from every patient. Diagnosis of otomycosis was made by the combination of presence otorrhea along with of one or more clinical symptoms (including ear itching, otalgia, fullness of ear, tinnitus and hypoacusis) and positive fungal culture of the secretions expressing in the external ear canal. Before allocation of group to the patients, baseline characteristics were documented including age, gender, body mass index (BMI), history of comorbid conditions, symptoms at presentation and composite pretreatment symptoms score and laterality of infection. Pretreatment symptoms score for each symptom at the time of data collection which was assessed based on numeric rating scale with score-0 being given if there were no symptoms, score-1 for mild, score-2 for moderate and score-3 for severe symptoms. After that all the individual scores were summed up to calculate composite symptoms score. Based on the laterality of infection, patients were allocated to their respective groups. Among patients who had infection in their right ear were allocated Group-A in which patients were treated with 1% terbinafine cream/lotion to be applied in the ear twice daily for a period of two weeks. Among patients who had infection in their left ear were allocated Group-B, in which patients were treated with 1% clotrimazole cream/lotion to be applied in the ear twice daily for a period of two weeks.

All patients were advised to keep their ears clean and dry, particularly after taking a bath. They were also advised to stop swimming during this period if they were avid swimmers. After two weeks of

treatment completion, patients were called for follow up to assess them for efficacy. Efficacy assessment was based on achievement of complete cure which was defined by composite symptoms score of 0 along with negative culture of the secretions from external ear canal. In case of failure of treatment (defined as positive fungal culture after two weeks of treatment), alternative treatment was provided to the patients as per culture and sensitivity report.

Data analysis was done through Statistical Package for Social Sciences (SPSS) version 22. Normality of quantitative data was checked by Shapiro-Wilk test which showed that age, BMI and composite symptoms score were not normally distributed and were thus presented as median with interquartile range (IQR). Qualitative variables (gender, history of comorbidities and efficacy) were presented using percentage and frequency. To compare the efficacy between study groups, Chi-square test was used with a p -value of ≤ 0.05 taken as statistically significant.

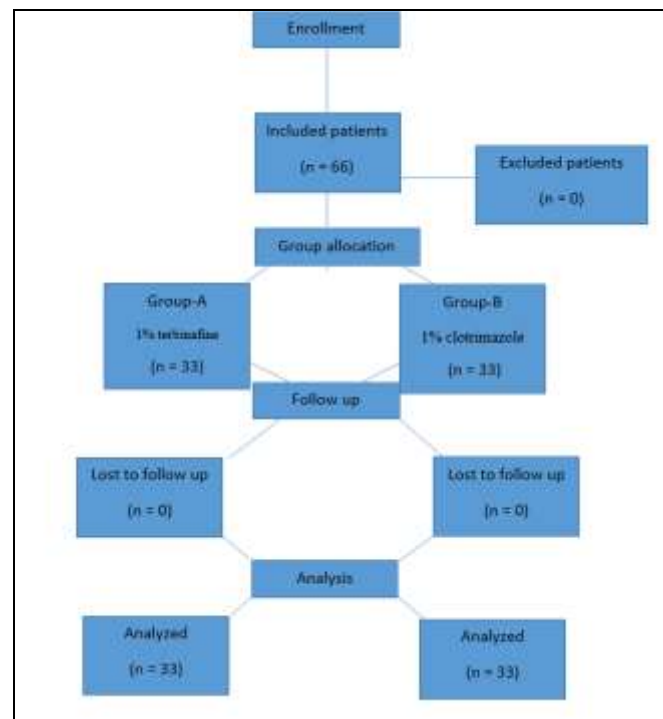


Figure-1: Consort Patient Flow Diagram (n=66)

RESULTS

In this study, 66 patients were included. Median age was 39.00(57.00–19.00) years. There were 24(36.36%) male and 42(63.64%) female patients. Median BMI was 29.85 (37.50 – 19.60) kg/m². There

were 35 (53.03%) patients who had diabetes, 7(10.61%) had hypertension and 7(10.61%) were smokers. Comparison of baseline characteristics between study groups is given in Table-I.

Table-I: Comparison of Baseline Characteristics between Study Groups (n = 66)

Parameter	Group-A (n = 33) n (%)	Group-B (n = 33) n (%)	p-value
Age in years (Median, IQR)	39.00 (57.00 - 19.00)	39.00 (54.00 - 19.00)	0.933
Gender			
Male	10(30.30%)	14(42.42%)	0.306
Female	23(69.70%)	19(57.58%)	
Body Mass Index (Median, IQR)	30.20 (34.70 - 19.60)	29.40 (37.50 - 21.30)	0.156
Comorbidity			
Diabetes	16(48.48%)	19(57.58%)	0.627
Hypertension	5(15.15%)	2(6.10%)	
Smoking	4(12.12%)	3(9.10%)	

Most common presenting symptom among patients diagnosed with otomycosis was ear itching 44 (66.67%) followed by otalgia 35(53.03%), tinnitus 22(33.33%), fullness of ear 11(16.67%) and hypoacusis 9(13.64%). Median pretreatment composite symptoms score was 3.00 (10.00-1.00). Comparison of distribution of presenting symptoms and median pretreatment composite symptoms score between groups is given in Table-II.

Table-II: Comparison of Distribution of Presenting Symptoms and Median Pretreatment Composite Symptoms Score Between Groups (n = 66)

Parameter	Group-A (n = 33) n (%)	Group-B (n = 33) n (%)	p-value
Ear itching	23(69.70%)	21(63.64%)	0.602
Otalgia	17(51.52%)	18(54.55%)	0.805
Tinnitus	10(30.30%)	12(36.36%)	0.602
Fullness of ear	3(9.10%)	8(24.24%)	0.099
Hypoacusis	3(9.10%)	6(18.18%)	0.292
Pretreatment composite symptoms score (Median, IQR)	3.00(7.00 - 1.00)	4.00(10.00-2.00)	0.082

In terms of efficacy, it was found that in Group-A (n=33), frequency of complete cure was 27(81.82%) while in Group-B (n=33), it was 16(48.48%); ($p=0.004$). Comparison of efficacy of 1% terbinafine and 1% clotrimazole in treatment of otomycosis is given in Table-III.

Table-III: Comparison of Efficacy of 1% Terbinafine and 1% Clotrimazole in Treatment of Otomycosis (n = 66)

Efficacy	Group-A (n = 33) n (%)	Group-B (n = 33) n (%)	p-value
Complete cure			
Yes	27(81.82%)	16(48.48%)	0.004
No	6(18.18%)	17(51.52%)	

DISCUSSION

Fungal infections are amongst the most difficult types of infection to treat in general medical practice owing to a lot of personal, environmental and social factors.^{12,13} One of the major factors that results in this difficulty to treat fungal infections is the ever-growing resistance against various anti-fungal agents on the global scale as well as in Pakistan.^{14,15} Otomycosis, the fungal infection of external ear canal, is a common disease entity encountered in the ENT departments which causes a myriad of troubling symptoms. This study focused on comparing the efficacy of two different treatment options for this fungal infection of the ear.

Upon analysis of the age of the patients who were diagnosed with otomycosis, average age of the patients was 39 years. Compared to this, Asoegwu *et al.* found that the median age of the patients suffering from otomycosis was relatively younger, reported at 29 years.¹⁶ Similarly, a review study conducted by Pereira *et al.* found that most cases of otomycosis occurred in the age range between seven to forty-four years.¹⁷ Upon analysis of the gender distribution of otomycosis, it was observed that majority of the sufferers of the fungal infection of the external ear canal were females making up 63.64% of the patients. This female predominance correlates with the findings reported in previous literature stating females to be affected more by otomycosis.¹⁸ An interesting finding observed in present study was a high proportion of the patients who had fungal infection of the external ear canal were found to have diabetes. This finding can be attributed to the fact that diabetes results in significant impairment of the immune system of the body making them highly immunocompromised which increases the chances of getting fungal infection.¹⁹

Most common presenting symptom was itching in the ear followed by otalgia, tinnitus, fullness of ear and hypoacusis. Compared to this, Sogebi *et al.* found distribution of presenting symptoms similar to the trend of distribution of clinical presentation being observed in present study.²⁰

Upon analysis of the efficacy of terbinafine compared with clotrimazole, present study found that terbinafine was significantly more efficacious as compared to clotrimazole in treatment of otomycosis (81.82% versus 48.48%, respectively, $p=0.004$). In a study by Xu *et al.*, it was observed that the efficacy of terbinafine in successfully treating otomycosis was

92.7% which was much higher yet comparable to the efficacy of terbinafine being observed in present study.²¹ Praveen *et al.* found that the frequency of good response by clotrimazole in treatment of fungal infection of the external ear canal by the end of two weeks of treatment was 75%, which was much higher compared to the efficacy being reported in present study.²² This difference can be due attributed to the differences in the anti-fungal resistance patterns in the demographics of both studies. Similar to the efficacy of clotrimazole in treating fungal ear infection being reported in present study, Shabbir *et al.* found that the efficacy of clotrimazole in otomycosis was 46.34%.²³

When it comes to head-to-head comparison of efficacy of terbinafine and clotrimazole in management of otomycosis, no study has been conducted to date, however, efficacy of these two drugs has been compared in the eradication of fungi that are involved in etiopathogenesis of otomycosis. In this instance, a study was conducted by Mohammed *et al.* in which a comparison of efficacy of terbinafine and clotrimazole was performed in eradication of fungal infection caused by dermatophytes (one of the causative agents in otomycosis).²⁴ They found no statistically significant difference between terbinafine and clotrimazole efficacy to successfully eradicate fungal infection ($p=0.354$). Similarly, in another study by Farah *et al.*, no significant difference was observed between efficacy of terbinafine and clotrimazole in successfully treating candida infection (another important causative pathogen of otomycosis).²⁵ Compared to this, the present study observed terbinafine to be significantly better than clotrimazole ($p=0.004$) but the difference in the initial diagnosis may be the reason of this difference in the results from the aforementioned studies.

Based on the results of present study, terbinafine comes out as a superior antifungal agent that should be preferred over clotrimazole for managing patients with otomycosis.

LIMITATIONS OF STUDY

One of the major limitations of present study was inclusion of only clotrimazole and terbinafine sensitive cases of otomycosis which does not answer an important question: which amongst these agents may be better if used as an empirical treatment? For this purpose, it is recommended to conduct further studies in this regard to explore all the aspects of these two antifungal drugs used for the treatment of otomycosis.

CONCLUSION

In conclusion, terbinafine should be used as a preferred pharmacological intervention in comparison to clotrimazole for treatment of otomycosis as evidenced by significantly higher efficacy of terbinafine in comparison to clotrimazole (81.82% and 48.48%, respectively, $p = 0.004$).

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MSZ & MT: Conception, study design, drafting the manuscript, approval of the final version to be published.

MAN & MD: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

GF & AH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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