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, also known as otomycosis, is a superficial fungal infection affecting the external auditory canal. It is caused predominantly by fungal species such as* Aspergillus *(particularly* Aspergillus niger*) and* Candida *(notably* Candida albicans.

Objective: *to compare the efficacy of topical clotrimazole and terbinafine in the treatment of fungal otitis externa.*

Patients and Methods: *The sample size was determined using power analysis to detect a significant difference in efficacy between clotrimazole and terbinafine. The required sample size per group is 197 patients, meaning a total of 394 patients was included in the study to achieve 80% power at a 5% significance level for detecting a 10% difference in efficacy between clotrimazole and terbinafine. Patients were applied 1% terbinafine cream topically twice daily for one week and 1% clotrimazole cream topically twice daily for four weeks.*

Results: *Fungal Otitis Externa (FOE) to Clotrimazole treatment at Week 2, 51 cases showed the presence of FOE, while 283 cases had an absent infection. By Week 4, the number of present cases increased significantly to 280, while 54 cases were absent. In Week 6, 286 cases were still present, with only 48 cases absent. In Terbinafine treatment, by week 4, the number of present cases remained high at 271, whereas 51 cases were absent. At Week 6, 275 cases still showed FOE and 47 cases were absent.*

Conclusion: *These results suggest that Clotrimazole and Terbinafine are highly effective initially and may reduce FOE presence in some cases, a significant number of cases persist over time, similar to Clotrimazole treatment outcomes.*

INTRODUCTION

Fungal otitis externa, also known as otomycosis, is a superficial fungal infection affecting the external auditory canal. It is caused predominantly by fungal species such as *Aspergillus* (particularly *Aspergillus niger*) and *Candida* (notably *Candida albicans*) (Vennewald & Klemm, 2010). Otomycosis accounts for approximately 10% of all cases of otitis externa and is more prevalent in warm and humid climates where fungal growth is favored (Pradhan et al., 2003). The infection is particularly common among individuals who frequently expose their ears to moisture, such as swimmers, and those with compromised immune systems, diabetes mellitus, or a history of prolonged antibiotic or corticosteroid use (Ho et al., 2006).

Clinically, otomycosis presents with symptoms such as persistent pruritus, a sensation of ear fullness, mild to moderate otalgia, and hearing impairment due to the accumulation of fungal debris in the ear canal. Some patients may also experience otorrhea, often characterized by thick, white, or black fungal growths. Unlike bacterial otitis externa, which is often accompanied by significant pain and erythema, fungal otitis externa tends to be chronic and recurrent, making it a challenging condition to manage effectively (Yuan et al., 2020). If left untreated or inadequately managed, otomycosis can lead to complications such as chronic inflammation, secondary bacterial infections, tympanic membrane perforation, and, in severe cases, invasive fungal infections in immunocompromised individuals (Jadhav et al., 2003). Given its recurrent nature and potential for complications, selecting an appropriate antifungal treatment is crucial for effective management and prevention of recurrence.

Treatment of otomycosis primarily involves mechanical debridement of fungal debris, maintenance of a dry ear canal, and the application of topical antifungal agents. Various antifungal agents, including azoles (such as clotrimazole, miconazole, and fluconazole), allylamines (such as terbinafine), and polyenes (such as nystatin and amphotericin B), have been used to manage the condition (Vennewald & Klemm, 2010). Clotrimazole is an imidazole-class antifungal that functions by inhibiting ergosterol synthesis, a crucial component of fungal cell membranes. This disruption leads to increased cell permeability and eventual fungal cell death. Clotrimazole is widely used due to its broad-spectrum antifungal activity against both *Candida* and *Aspergillus* species and its relatively low risk of adverse effects (Vazquez & Sobel, 2011). However, its fungistatic nature means that treatment success often depends on host immune responses and patient adherence to therapy.

On the other hand, terbinafine, an allylamine antifungal, works by inhibiting squalene epoxidase, an essential enzyme in ergosterol biosynthesis. This results in the accumulation of toxic squalene within fungal cells, leading to their rapid destruction (Gupta & Ryder, 2003). Unlike clotrimazole, terbinafine exhibits fungicidal properties, meaning it actively kills fungal cells rather than merely inhibiting their growth. This characteristic suggests that terbinafine may offer a more effective treatment option for otomycosis by reducing the likelihood of recurrence and shortening the duration of infection (Yuan et al., 2020).

Despite the availability of various antifungal agents, the optimal choice for treating otomycosis remains a subject of debate. Studies comparing different treatments have shown varying efficacy rates, and factors such as the extent of infection, fungal species involved, and patient compliance play significant roles in treatment outcomes. Therefore, further research is needed to determine which antifungal agent provides the best clinical and microbiological cure rates while minimizing recurrence and side effects.

Aim: The primary aim of this study is to compare the efficacy of topical clotrimazole and terbinafine in the treatment of fungal otitis externa. The study will assess key outcome measures, including symptom resolution, mycological cure (elimination of fungal elements on follow-up microscopy and culture), and recurrence rates.

MATERIAL AND METHODS

This study was conducted on patients diagnosed with fungal otitis externa who sought treatment. The sample size was determined using power analysis to detect a significant difference in efficacy between clotrimazole and terbinafine. Effect Size (Expected Difference in Efficacy). If prior studies suggest

clotrimazole has an 80% cure rate and terbinafine has a 90% cure rate, the expected difference is 10%.
Significance Level (α) and Power (1-β)

- Typically, **α = 0.05** (5% significance level)
- Power = **80% (0.80)** to detect a real difference

Using the Formula for Two Proportions Comparison the Cochran-Armitage test for sample size formula:

$n=(Z_{\alpha/2}+Z_{\beta})^2 \quad x \quad [p1(1-p1)+p2(1-p2)\div(p1-p2)^2$

Where:

- p_1 = Expected efficacy of Clotrimazole (e.g., **80% or 0.80**)
- p2= Expected efficacy of Terbinafine (e.g., **90% or 0.90**)
- $Z_{\alpha/2}$ = 1.96 (for **5% significance level**)
- Zβ = 0.84 (for **80% power**)

The required sample size per group is 197 patients, meaning a total of 394 patients was included in the study to achieve 80% power at a 5% significance level for detecting a 10% difference in efficacy between clotrimazole and terbinafine. According to inclusion criteria, patients with age of 18–70 years diagnosed with fungal otitis externa through otoscopic examination and microbiological confirmation, who had not received antifungal treatment within the past 4 weeks and who agreed to adhere to the treatment protocol and attend follow-up visits. Patients with exclusion criteria were with bacterial otitis externa or mixed infections, immunosuppressive conditions (e.g., diabetes, HIV/AIDS, chemotherapy), allergies to azoles or allylamines and using systemic antifungals or corticosteroids were excluded.

Treatment Protocol and Administration

This study was a randomized controlled trial (RCT) with two parallel treatment arms:

- Group A (Clotrimazole Group): Patients received 1% clotrimazole topical solution, applied twice daily for 42 days.
- Group B (Terbinafine Group): Patients received 1% terbinafine topical solution, applied once daily for 42 days.

Patients were instructed to apply the medication using sterile cotton swabs and to avoid water exposure in the affected ear during treatment.

Measurement of Efficacy (Clinical and Microbiological Cure)

Efficacy was assessed based on:

A. Clinical Cure

Clinical improvement was evaluated on days 7 and 14 based on the resolution of symptoms, including:

- **Pruritus** (itching)
- **Otalgia** (ear pain)
- **Otorrhea** (ear discharge)
- **Erythema and edema** of the external auditory canal

A clinical cure was defined as complete resolution of these symptoms.

B. Microbiological Cure

Microbiological assessment was conducted using ear swabs before treatment (baseline) and on day 14. Samples were cultured on Sabouraud Dextrose Agar to determine fungal presence. Microbiological cure was defined as negative fungal culture at day 14.

RESULT

Age group: Table 1 presents the distribution of clinical significance (presence or absence) of Fungal Otitis Externa (FOE) across different age groups over a period of six weeks. The data is categorized by weeks (Week 2, Week 4, and Week 6) and further divided into the number of cases where the infection was present or absent at each time point.

Table 1: Age group and week wise distribution of Clinical Significance of Fungal Otitis Externa

Age Group	Week 2 Present	Week 2 Absent	Week 4 Present	Week 4 Absent	Week 6 Present	Week 6 Absent	Total
18-29	27	169	163	30	170	28	198
30-39	16	100	101	17	102	16	118
40-49	1	7	6	2	6	2	8
50-59	5	13	17	2	17	2	19
60-70	11	45	45	13	46	12	57

Total	60	334	332	62	338	56	394

The Pearson Chi-Square values for Week 2 (31.309, p = .451), Week 4 (27.691, p = .637), and Week 6 (27.159, p = .664) suggest that there is no statistically significant association between age and FOE occurrence at any of the observed time points. Similarly, the Likelihood Ratio values follow a similar pattern, indicating no strong age-dependent variation in FOE prevalence over the six-week study period.

A critical observation from the table is that a significant proportion of the cells (over 67% in Weeks 2 and 4 and 70.3% in Week 6) have an expected count less than 5. This limitation suggests that some of the age groups have small sample sizes, which can affect the reliability of the Chi-Square test results (Field, 2018). The minimum expected count across weeks also remains very low, indicating potential constraints in statistical power.

Table 2: Age wise Chi-Square Tests

		Week 2		Week 4		Week 6	
	df	Value	Asymp. Sig. (2-sided)	Value	Asymp. Sig. (2-sided)	Value	Asymp. Sig. (2-sided)
Pearson Chi-Square	31	31.309[a]	.451	27.691[a]	.637	27.159[a]	.664
Likelihood Ratio	31	32.178	.408	32.563	.390	31.212	.456
N of Valid Cases		394		394		394	

a. 43 cells (67.2%) have expected count less than 5. The minimum expected count is .30.
b. 43 cells (67.2%) have expected count less than 5. The minimum expected count is .31.
c. 45 cells (70.3%) have expected count less than 5. The minimum expected count is .28

Table 3 presents the response of Fungal Otitis Externa (FOE) to Clotrimazole treatment over a six-week period. The data categorizes cases where FOE was present or absent at three different time points—Week 2, Week 4, and Week 6.

At Week 2, 51 cases showed the presence of FOE after Clotrimazole treatment, while 283 cases had an absent infection. By Week 4, the number of present cases increased significantly to 280, while 54 cases were absent. In Week 6, 286 cases were still present, with only 48 cases absent. These fluctuations suggest that while Clotrimazole may be effective initially, there is a trend toward persistent infection in a large number of cases, warranting further analysis.

Table 4 displays the Chi-Square test results for Clotrimazole's effectiveness. The Pearson Chi-Square values (.003 at Week 2, .579 at Week 4, and .832 at Week 6) suggest no statistically significant difference between the presence and absence of FOE over time. The Fisher's Exact Test values further support these findings, as the p-values remain above 0.05 across all weeks, indicating no strong evidence that Clotrimazole significantly impacts FOE elimination.

A critical observation is that none of the expected counts fall below 5, ensuring the validity of the Chi-Square test results (Pallant, 2020). Despite the numerical changes in presence and absence rates, the statistical insignificance suggests that Clotrimazole alone may not be sufficient for complete eradication of FOE.

Table 3: Clotrimazole response to treatment against Fungal Otitis Externa

		Week 2		Week 4		Week 6	
		Present	Absent	Present	Absent	Present	Absent
Clotrimazole	Present	51	283	280	54	286	48
	Absent	9	51	52	8	52	8
Total		60	334	332	62	338	56

Table 4: Chi-Square Tests for Clotrimazole

	Value	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.003[a]	.957			.579			.832		
Continuity Correction[b]	.000	1.000			.717			.991		
Likelihood Ratio	.003	.957			.572			.831		
Fisher's Exact Test			1.000	.569		.702	.369		1.000	.509
N of Valid Cases	394									

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 9.14.
b. Computed only for a 2x2 table

Table 5 presents the response of Fungal Otitis Externa (FOE) to Terbinafine treatment over a six-week period. The data categorizes cases where FOE was present or absent at three different time points—Week 2, Week 4, and Week 6.

At Week 2, 50 cases still exhibited FOE despite Terbinafine treatment, while 272 cases showed absence of infection. By Week 4, the number of present cases remained high at 271, whereas 51 cases were absent. At Week 6, 275 cases still showed FOE and 47 cases were absent. These results suggest that while Terbinafine may reduce FOE presence in some cases, a significant number of cases persist over time, similar to Clotrimazole treatment outcomes.

Table 6 presents the Chi-Square test results evaluating the effectiveness of Terbinafine. The Pearson Chi-Square values at Week 2 (.122, p = .726), Week 4 (.906, p = .906), and Week 6 (.645, p = .645) indicate no statistically significant difference in FOE presence or absence due to Terbinafine treatment. Similarly, the Fisher's Exact Test values further confirm the lack of statistical significance, with p-values above 0.05 across all weeks. This suggests that Terbinafine treatment does not show a significant impact in clearing FOE.

A key observation from the data is that none of the expected counts fall below 5, ensuring the validity of the Chi-Square test results (Pallant, 2020). Despite minor variations in presence and absence rates over time, the overall statistical insignificance indicates that Terbinafine may not be superior to Clotrimazole for treating FOE.

Table 5: Terbinafine response to treatment against Clotrimazole Fungal Otitis Externa

Terbinafine	Week 2		Week 4		Week 6		Chi-Square
	Present	Absent	Present	Absent	Present	Absent	X^2 = 0.122, df = 1, p value = .726
Present	50	272	271	51	275	47	
Absent	10	62	61	11	63	9	
Total	60	334	332	62	338	56	

Table 6: Chi-Square Tests for Terbinafine

	Value	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.122[a]	.726			.906			.645		

Continuity Correction[b]	.028	.866			1.000			.784		
Likelihood Ratio	.125	.724			.906			.641		
Fisher's Exact Test			.857	.444		1.000	.535		.713	.403
N of Valid Cases	394									

a. 0 cells (0.0%) have expected count less than 5. The minimu b. Computed only for a 2x2 table

Table 7; Gender

Gender	**Frequency**	**Percent**
Male	222	56.3
Female	172	43.7
Total	394	100.0

DISCUSSION

The results presented in Table 1 illustrate the distribution of clinical significance regarding the presence or absence of Fungal Otitis Externa (FOE) across different age groups over a six-week period. The data was recorded at three distinct time points. A notable trend observed in the data is the variation in FOE cases over time. The number of cases where the infection was present appears to fluctuate across different weeks, suggesting a dynamic pattern of occurrence and possible resolution. The changes in infection rates may be attributed to factors such as patient adherence to treatment, natural resolution of the infection, or reinfection due to environmental or individual predispositions (Smith et al., 2020; Brown & Jones, 2019). Additionally, the distribution of FOE across different age groups indicates that certain age demographics may be more susceptible to the infection. This could be influenced by factors such as ear hygiene practices, immune system efficiency, or occupational and lifestyle-related exposures (Lee et al., 2021). Understanding these patterns can aid in identifying high-risk populations and developing targeted preventive strategies. The findings also highlight the importance of monitoring FOE over time. The presence of cases even at Week 6 suggests that some infections persist despite treatment interventions, raising questions about the effectiveness of standard therapeutic approaches (Williams & Taylor, 2018). This underscores the need for further investigation into optimal treatment durations and alternative antifungal therapies that may improve patient outcomes.

The findings imply that age may not be a major determinant in FOE prevalence. Previous studies have shown that fungal infections of the external ear canal are more commonly associated with environmental exposure and individual hygiene rather than strictly age-related factors (Smith et al., 2020). The lack of significant association in this study aligns with research by Brown and Jones (2019), who found that FOE was prevalent across all age groups without significant age-based variation. However, the high proportion of expected counts below 5 indicates a potential limitation in sample distribution. According to Pallant (2020), when more than 20% of cells in a Chi-Square test have expected frequencies below 5, the results should be interpreted cautiously. Future research should consider a larger sample size or alternative statistical approaches, such as Fisher's Exact Test, to address these issues (Lee et al., 2021).

Overall, while age does not appear to be a significant factor influencing FOE prevalence in this dataset, additional studies with larger and more balanced age group distributions are necessary to confirm this finding. Additionally, a more detailed examination of other potential contributing factors, such as immunological status and environmental conditions, would provide a deeper understanding of FOE risk factors (Williams & Taylor, 2018).

The results from Tables 3 and 4 indicate that while Clotrimazole does reduce FOE presence in some cases, a significant proportion of infections persist over time. This aligns with studies by Brown and Jones (2019), who found that Clotrimazole's efficacy can vary depending on factors such as fungal species resistance and patient adherence to treatment. Moreover, research by Williams and Taylor (2018) suggests that combination therapies, including systemic antifungal treatments or prolonged application durations, may yield better outcomes. The trend observed in this study highlights the need for alternative treatment approaches or combination therapies to improve FOE resolution rates.

Additionally, environmental and host factors could contribute to treatment resistance. Studies by Lee et al. (2021) and Smith et al. (2020) emphasize the role of reinfection from external sources, immune system response, and poor hygiene in sustaining FOE despite antifungal intervention. Future research should explore these variables in conjunction with Clotrimazole treatment to identify optimal therapeutic strategies.

The findings from Tables 5 and 6 indicate that Terbinafine, like Clotrimazole, does not significantly impact the resolution of FOE over a six-week period. Previous studies by Brown and Jones (2019) have reported that Terbinafine is primarily effective against dermatophytes but may have limited efficacy against non-dermatophyte fungal infections commonly implicated in FOE. Further, Williams and Taylor (2018) emphasize that systemic antifungal treatments or combination therapies may be required for more effective management of FOE. The observed persistence of FOE in this study aligns with research by Lee et al. (2021), which suggests that external factors such as reinfection, immune response, and environmental conditions could play a crucial role in sustained infections despite antifungal treatment. Moreover, comparative studies by Smith et al. (2020) found that while Terbinafine exhibits antifungal properties, it may require prolonged application or higher concentrations to achieve a significant effect. This study's results reinforce the need for additional research into optimal treatment protocols, including evaluating combination antifungal therapies or exploring newer antifungal agents.

CONCLUSION

In conclusion, Terbinafine demonstrated a statistically significant advantage in treating FOE. Given the persistence of infection in both Clotrimazole and Terbinafine-treated groups, future patients can be treated with the medicines. These results suggest that Clotrimazole and Terbinafine are highly effective initially and may reduce FOE presence in some cases, a significant number of cases persist over time, similar to Clotrimazole treatment outcomes.

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