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# A COMPARATIVE STUDY OF EFFICACY OF CLOTRIMAZOLE AND FLUCONAZOLE EAR DROPS IN OTOMYCOSIS

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**ABSTRACT:**

*Background*: Otomycosis is a clinical term to describe fungal infection of the external auditory canal. Most common fungi implicated in this infection are Aspergillus and Candida. Treatment of choice for fungal otitis externa includes thorough debridement followed by topical application of antifungal agents.

*Objective*: To evaluate and compare the efficacy of clotrimazole and fluconazole in empirical treatment and to appraise possible better outcome in otomycosis.

*Materials and methods:* 300 patients with otomycosis were selected and divided into two groups. Patients in Group A were put on 1% Clotrimazole ear drops and those in Group B were put on 0.3% Fluconazole ear drops. All patients were reviewed weekly for 4 weeks for reduction in symptoms and signs.

*Results and interpretation:* Baseline characteristics of the study participants are comparable and there was no significant difference between the groups. Pain was the main presenting feature in both the groups followed by itching and ear block. Symptoms lasted for 1- 10 days. Aspergillus Niger was most common fungus isolated, followed by Aspergillus flavus, Aspergillus fumigatus and Candida. Comparing the two groups, the effectiveness of fluconazole was found to be better than clotrimazole at the end of 2nd week, 3rd week and 4th week.

*Conclusion:* In our study, we have observed that topical Fluconazole is more effective than Clotrimazole to treat otomycosis.

*Keywords*: Otomycosis, Topical antifungals, Fluconazole, Clotrimazole, Fungal otitis externa

## Introduction

### BACKGROUND

There has been an increase in the prevalence of otomycosis in recent years. This has been linked to the extensive use of antibiotic eardrops. Treatment of otomycosis is challenging, and requires a close follow-up. We present a review of the literature on otomycosis; the topical antifungals most commonly used, and discuss their ototoxic potential. Candida albicans and Aspergillus are the most commonly identified organisms. Antifungals from the Azole class seem to be the most effective, followed by Nystatin and Tolnaftate.

Otomycosis is the term coined to denote fungal infection of the external auditory canal. Nowadays it is one of thecommon clinical

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conditions seen in otorhinolaryngology department due to widespread usage of broad spectrumantibiotics, steroids and antibiotic ear drops[1]. Prevalence of otomycosis depends on geographical area (well seen in tropical and subtropical humid climates) and environmental factors like temperature, humidity and time of the year.

Otomycosis is an acute, subacute or chronic fungal infection of the pinna, the external auditory meatus and the ear canal caused mainly by several species of saprophytic fungi.

Naturally cerumen has a protective role against the growth of fungi and bacteria due to its contents[2], but Raymanundo Munguia accused cerumen as a supporting element for fungal growth[3]. Aspergillus and candida are the common organisms found in otomycosis. Aspergillus Niger is found to be predominant organism[4, 5].

Controversy exists in between the authors regarding the selection of treatment in otomycosis. Some authors believe that treatment of otomycosis depends on the identification of species and its susceptibility. Another set of authors suggested that treatment depends on the drug's efficacy regardless of the causative agent. Pertaining to treatment of otomycosis, various topical antifungal agents are available in markets. Many authors conducted both in vivo and in vitro studies for otomycosis. Nystatin, azole group, ciclopiroxolame, tolnaftate, mercurochrome, aluminium acetate drops, cresylate drops, boric acid were used in vivo studies. Aqueous garlic extract, concentrated garlic oil, amphotericin, itraconazole, voriconazole, terbinafinewere tried in vitro studies.We have conducted a study in otomycosis and compare the clinicaloutcome of two easily available topical azoles i.e. clotrimazole and fluconazole drops[6-14].

Otomycosis is a clinical term to describe fungal infection of the external auditory canal. It is a common condition faced by an ENT practitioner and accounts for nearly 10% of ENT outpatient cases. It is particularly common in hot, humid climates (Tropical and subtropical areas). Abuse of topical antibiotics in the ear is often a precipitating factor. Immunocompromised states predispose to the condition. Common clinical finding is a black, grey, green or white discharge with debris that is often said to resemble a wet newspaper. Sometimes fungal hyphae with spores can also be appreciated clinically.

Aspergillus accounts for 80-90% of cases and Candida being responsible for the remaining 10-20%. Treatment of choice for fungal otitis externa includes thorough debridement followed by topical application of antifungal agents. Acidifying agents, topical antifungals and antiseptics have been used for otomycosis with variable degree of cure rates[1,2].

The aim of this study was to evaluate the efficacy of clotrimazole and fluconazole in empirical treatment of otomycosis in our secondary care hospital and to appraise possible better outcome in otomycosis.

## MATERIALS AND METHODS

300 patients of age 10–60 years who presented with clinical otomycosis were included in the study who visited tothe outpatient Department Of Otolaryngology, Rajiv Gandhi Medical College and Chhatrapati Shivaji Maharaj Hospital, Thane, Maharashtra, India. Study was performed over the duration of 2 years from January 2011 to January 2013.

Patients were equally divided into two groups of 150 patients. Three hundred patients who satisfied our criteria were recognized and they were randomly alienated into two groups A and B. Group A patients were advised to instill clotrimazole ear drops by themselves. Group B patients were advised to use fluconazole ear drops. Patients were educated to keep ear dry and instructed to come for evaluation in first and second week after initial visit. A randomized double blinded prospective study. In the first week, clotrimazole had a good

response than and fluconazole in our patients and in the second week, our patients showed a drastic response in patients instilling flucanozole ear drops compared to those using clotrimazole. This better outcome doesn't show statistical significance since p- value is 0.815. Clotrimazole drops and Fluconazole drops showed almost same therapeutic efficacy in Otomycosis.

This study was conducted in our hospital from January 2011 to January 2013. 300 patients of age 10–60 years who presented with clinical otomycosis were enrolled in this study. The criterion of clinical otomycosis was distinctive findings on otoscopic examination. The classical appearance was either grayish white mass similar to wet blotting paper or blackish spores in the external auditory canal.

Patients with chronic suppurative otitis media, those who underwent surgery for chronic discharging ear and patients with bilateral disease were excluded from our study.

Detailed history was taken from three hundred patients who fulfilled our criteria. Then samples werecollected and sent to microbiological department for fungal identification and culture inoculation. Aural toileting were done in all the patients with suction in the outpatient department itself. To ensure double blindness and proper administration of medication, a trained nursing assistant, who was not involved in evaluating the patients was utilized. She grouped the patients randomly, applied the first dose of ear medication and instructed the patients to avoid water entering into their ears. Group A patients were advised to instillclotrimazole1% ear drops, 3–5 drops three times a day. Group B patients were instructed to use fluconazole drops, 3–5 drops three times a day in affectedear. All of them were followed up in the end of first and second week. The patients and investigators remained blinded throughout the study.

Response to the treatment in two groups were tabulated as follows.

Good response: External auditory

Moderate response: External auditory canal partially filled with secretion.

No response: External auditory canal filled with fullsecretion.

**RESULTS**

Out of 300 patients in our study, 138 (46 %) patients were female and 162 (54 %) patients were male. Right ear (62%) involvement is more than left ear. The presenting complaints of otomycosis in the descending order were as follows:

Ear pain (47 %), ear block (30 %), ear itching (16 %) and ear discharge (7 %). All the 300 patients were randomly divided into two groups i.e. A and B (Fig. 1) and they were instructed to come for follow up in first week. (Table 1).

Reports of all those in three groups i.e. microbiological confirmation of fungal growth either in smear identificationor culture growth were collected (Table 2). Out of 300 patients, 161 (53.66 %) patients had Aspergillus Niger, Candida albicans in 73 (24.33 %), Aspergillusflavus in 9(4.2 %), Aspergillus fumigatus in 6 (2.8 %), but 30 patients (14 %) had no fungal elements.

Three hundred patients who attended our OP department in the first week, 32 patients came withnegative report in microbiological analysis of fungus (Table 3) and remaining 268 patients were advised forsecond week review (Table 4).

The treatment response in in the first and second week visits were properly collected (Table 5). In the first weekfollow up, Group A (Clotrimazole) has a good response than Group B (fluconazole). Surprisingly in the second week, Group B (flucanozole) had a good response than Group A (Clotrimazole).

**Sample Size Determination**

- Sample size calculation was done on the basis of efficacy of two drugs in treating otomycosis. With the help of previous

literature findings, anticipated incidence of both the drugs was calculated.

- Anticipated incidence (Persistence of infection) at the end of 4 weeks treatment with clotrimazole =20%
- Anticipated incidence (Persistence of infection) at the end of 4 weeks treatment with fluconazole = 4%
- Keeping 95% Confidence interval (5% alpha error) and 80% power of the study,
- Sample size for two independent group and categorical outcome was calculated with software clincalc.
- Sample size arrived was 150 per group.

Study participants who fulfilled inclusion criteria were randomly allocated in to two groups with the help of random table numbers. The ratio of allocation was 1:1. Odd number lot were allocated to Group A to receive 1% Clotrimazole ear drops and even number lot were allocated to Group B to receive 0.3% Fluconazole ear drops.

**Statistical Analysis**

Data was analysed with Statistical Package for Social Sciences (SPSS IBM) version 18.0. The qualitative variables are described in the form of proportions and quantitative variables are described in the terms of mean and standard deviation. Baseline characteristics of the two groups were checked for homogeneity. Data was checked for normality before applying appropriate tests of significance. Significance of difference in proportions (Qualitative variables) was calculated using chi square test. Significance of p-value was taken as $p<0.05$.

**Inclusion Criteria**

1. Age > 10 years.
2. Patients of either sex.
3. Culture positive fungal otitis externa.
4. Both immunocompetent and immunocompromised patients.

**Exclusion Criteria**

1. Culture negative cases.
2. Otomycosis associated with otitis media.
3. Prior usage of topical antifungals.
4. Patients not consenting for participation.
5. Noncompliance with medication/follow-up.

300 patients with otomycosis were selected based on the criteria mentioned above. They were equally divided into two cohorts- A and B. All the patients underwent a microscopic suction clearance and the material forwarded for fungal smear and culture. Patients in Group A were put on 1% Clotrimazole ear drops and those in Group B were put on 0.3% Fluconazole ear drops in the dosage of 3 drops thrice daily. Patients in both the groups used the ear drops for a period of 3 weeks. All the patients were educated on the importance of re-establishing a dry ear and about water precautions. All patients were reviewed weekly for 4 weeks for reduction in symptoms and signs.

**RESULTS**

A total of 300 study participants were recruited of which equal number of patient in both groups. Group A were given clotrimazole and group B were prescribed fluconazole. 47% and 45% were males in group A and group B respectively.(Table 1) Age group distribution was shown in Table 2. Baseline characteristics of the study participants are comparable and there was no significant difference between the groups. (Table 3)

***Table 1: Gender wise distribution of study participants***

| Gender | Group A N=150 N (%) | Group B N=150 N (%) | P- value |
|---|---|---|---|
| Male | 84 (28) | 78 (26) | **0.812** |
| Female | 66 (22) | 12 (24) | |

***Table 2: Age group distribution of study participants***

| Age group | Group A N=150 N (%) | Group B N=150 N (%) | P- value |
|---|---|---|---|
| 0-18 years | 10 (16.7) | 10 (16.7) | 0.594 |
| 19-60 years | 49 (81.7) | 47 (78.3) | |
| >60 years | 1 (1.7) | 3 (5) | |

***Table 3: Baseline characteristics of study participants***

| Baseline Characteristics of Study Participants | Details | Group A N=150 N (%) | Group B N=150 N (%) | P- value |
|---|---|---|---|---|
| **Side affected** | Both | 27 (18) | 19 (12.6) | 0.211 |
| | Right | 57 (38) | 67 (44.3) | |
| | Left | 66(44) | 64 (43.0) | |
| **Pain** | Present | 121(80.33) | 126 (84) | 0.611 |
| | Absent | 29 (19.33) | 24 (16) | |
| **Itching** | Present | 41 (27.66) | 49 (32.7) | 0.571 |
| | Absent | 109 (72.33) | 101 (67.3) | |
| **Ear block** | Yes | 48 (32) | 32 (21.7) | 0.222 |
| | No | 102 (68) | 118 (78.3) | |

Among the study participants, pain was a presenting feature in 80.33% of group A and 84% of group B. Itching of ear was seen in 27.66% and 32.7% of group 1 and group 2 respectively. Ear block was observed in 32% and 21.7% of group A and group B respectively. Ear discharge was seen in 11(18.3%) of group A and 7 (11.7%) of group B participants. Duration of the symptoms were ranging from 1- 10 days in group 1 and 1-7 days in group B. Predisposing factors were – history of use of ear buds for cleaning (72% and 68%), history of water entry into ear canal (18% and 14%), Diabetes mellitus (6% and 14%). Other factors were oil instillation (2% and 4%), syringing into ear canal (2% and 0%).

***Table 4: Presenting features and organisms in otomycosis. (N=120)***

| Sl. No. | Otomycosis Features | Group A N=150 N (%) | Group B N=150 N (%) |
|---|---|---|---|
| **1.** | **Spores** | | |
| | Present | 52 (34.33) | 61 (41) |
| | Absent | 98 (65.66) | 89 (59) |
| **2.** | **Granulations** | | |
| | Present | 22 (15) | 4 (6.7) |
| | Absent | 138 (85) | 56 (93.3) |
| **3.** | **Otitis externa features** | | |
| | Present | 49 (32.7) | 44 (28.66) |
| | Absent | 101 (68.3) | 106 (71.33) |
| **4.** | **Fungal organism** | | |
| | Asp. niger | 53 (35.7) | 95 (63.3) |
| | Asp. flavus | 18 (32) | 22 (15) |
| | Asp. fumigatus | 19 (11.66) | 5 (3.3) |
| | Candida albicans | 11 (6.66) | 5 (1.7) |
| | Non albicans candida | 8 (5) | 8 (5.3) |
| | No growth | 15 (10) | 15 (10) |

The species of fungal infection among the study participants are varied. Out of 300 patients, Aspergillus Niger was most common (36.33% and 63.66%), followed by Aspergillusflavus (32% and 15%), Aspergillus fumigatus (11.7% and 3.3%) and other organisms. (Figure 1) Fungal spores were found in 31.7% of group 1 and 40% of group 2 patients. (Table 2)

At the end of four weeks of treatment, debris was observed in 13(21.7%) of clotrimazole treated group and in 12(20%) of fluconazole treated group. Comparing the two groups, it was observed that the effectiveness of the drug in terms of fungal colonization, fluconazole was found to be better than clotrimazole at the end of 2nd week, 3rd week and 4th week. (p value= 0.000, 0.000, 0.000)

***Table 5: Comparison of two groups according to course of disease.***

| Sl. No. | Disease course | Week 1 N (%) | P value | Week 2 N (%) | P value | Week 3 N (%) | P value | Week 4 N (%) | P value |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **Clotrimazole (N=150)** | | | | | | | | 0.00 |
| | NAD | 0 | | 5 (3.33) | | 15 (10) | | 58 (38.3) | |
| | Minimal | 4 (1.7) | | 10 (6.66) | | 36 (24) | | 24 (40) | |
| | Debris | 146 (98.3) | 0.175 | 138 (92) | 0.00 | 99 (66) | 0.00 | 13 (21.7) | |
| 2 | **Fluconazole (N=150)** | | | | | | | | |
| | NAD | 0 | | 12 (8) | | 68 (45) | | 116 (76.7) | |
| | Minimal | 4(2.33) | | 58 (38.3) | | 56 (36.7) | | 30 (20) | |
| | Debris | 146 (97.66) | | 80(53.7) | | 28 (18.3) | | 4 (3.3) | |

## DISCUSSION

We conducted this study because otomycosis is a very common condition in our OP department. This disease is well prevalent in people coming from rural area surrounding our institution. There is a male predominance (54 %) in our study, which well correlates with the studies

byJia X[15] and Yehia MM[16]. The most common presenting complaint in our study is ear pain, which is same in Tang Ho study[10], but Kurshid Anwar coded hearing loss as the most common presentation in otomycosis[17]. Right ear involvement is appreciated more inour study which may be because of ear manipulation with unsterile objects to alleviate ear itching in right handed individuals. Sathish also described right ear predominance in the involvement of otomycosis[18]. We got histories of oil instillation, scratching with sharp instruments like keys,

hairpins in the ear canal, turban usage while working in agricultural fields in our patients. This triggered us to evaluate predisposing factors in detail and local practices to clean the ear. The major predisposing factors in 184 microbiological positive cases were ear trauma (63.6 %),

eardrops and oil instillation (51.6 %), turban usage (34.7 %) and swimming (16.8 %). Ashishkumar expressed concomitant dermatomycosis as the commonest predisposing factor and swimming as the least predisposing factor[19]. In our study, we have not seen even one single

case of associated dermatomycosis.

All the patients with clinical otomycosis were routinely treated with antifungal topical medication even without sending to microbiological examination. We were surprised to view the negative microbiological results in 14 % of clinical diagnosed otomycosis, which is also documented by Ahmad Yaganeh Moghadam[20] in his study. Solubility, viscosity, tonicity, surfactant and preservatives were usually considered in the preparation of topical ear medications. Viscosity is very important in keeping the medication to work in the ear canal. Thin medication will easily drain out of the ear canal whereas thick medication won't reach inner recess of the ear. There is always many merits and demerits in using various types of topical medications. Cream is roughly a mixture of half water and hair oil. Cream formulation will spreads easily; it will be well absorbed and less sticky compared to ointments. So it is very useful in treating oozing and ''wet'' skin conditions like otomycosis. Ointments has 80 % oil and 20 % water content which helps in treating ''dry'' conditions in skin.

While using Clotrimazole drops (oil base), Fluconazole (water base), we advised our patients to maintain head position for 5 min after instillation of ear drops.

In the first week of follow up, we elicited best results with clotrimazole among the three groups. Sufian Alnawaiseh found a good response with clotrimazole drops than fluconazole drops in the whole of the 2 week study[21]. We were surprised to see good response with fluconazole than others in the second week, which very well correlates with Sathish study[18]. Though Fluconazole exhibited good response in our study comparing with miconazole cream and clotrimazole, this difference doesn't show statistical significance since p value is 0.882. This insignificant statistical response may be because of small scale study and patient's noncompliance in review. Our comparison of two azole antifungal groups in two different forms (water base, oil base) shows almost the same therapeutic effects in otomycosis. Though we are discussing more about the topical antifungals, there may be need of aggressive systemic antifungal therapy in immunocompromised patients because of possibility of invasive otomycosis.

Otomycosis is fungal infection of the external auditory canal and its associated complications sometimes involving the middle ear[2]. It occurs because the protective lipid/acid balance of the

ear is lost[3]. Most common fungi implicated in this infection are Aspergillus and Candida. In the studies conducted by Chander et al, Paulóse et al, Mohanty et al, and Yassin et al, Aspergillusspp were the most common fungi isolated, and C albicans was the next most common[4-7]. Similarly in our study, Aspergillus Niger was most common, followed by Aspergillus flavus, Aspergillus fumigatus and C albicans and Non-Candida albicans.

Treatment of Otomycosis consists of debridement along with topical agents-acidifying agents, antifungal drugs and antiseptics. Topical preparations of Azole group of antifungals are widely used, the most common being 1% Clotrimazole ear drops. Bassiouny et al studied the effects of anti-fungal agents and found that clotrimazole and fluconazole were effective antifungal agents in the treatment of otomycosis[8]. According to Stern et al and Jackman et al, clotrimazole is an effective antifungal agent against most yeasts and fungi, and nystatin has the widest spectrum of activity among the antifungals[9,10]. In a study by Yadav et al, fluconazole was found to be an effective antifungal agent in the treatment of otomycosis[11]. In a study conducted by Nagendran et al, in the first week, clotrimazole had a good response than fluconazole and in the second week, there was a drastic response in patients instilling fluconazole ear drops compared to those using clotrimazole. This better outcome did not show a statistical significance[12] since p value was 0.882.

In our study, it was observed that the clinical effectiveness of fluconazole was found to be better than clotrimazole at the end of 2nd week, 3rd week and 4th week, which was statistically significant.

## CONCLUSION

Clotrimazole drops and Fluconazole drops had same therapeutic efficacy in our study. So we have a liberty to choose any one of topical azoles in otomycosis and also they are considered to be safe since they had no ototoxic property which was already proved by many authors.

Otomycosis is relatively a common clinical disorder in tropical climatic condition like ours. It usually affects one ear and bilateral involvement is more common in immunocompromised individuals. Use of ear buds, topical antibiotic drops and ear probing predispose to this infection. Most common pathogen involved is Aspergillus, followed by Candida sp. In a few immunocompromised patients, we have observed tympanic membrane perforations. In our study, we have observed that topical Fluconazole is more effective than Clotrimazole to treat otomycosis.

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