

The Comparison of Clinical Aspects of Topical Clotrimazole 1% Cream and Natamycin 5% Ear Drops in the Treatment of Otomycosis

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Magna Scientia Advanced Biology and Pharmacy, 2025, 16(01), 031-037

Publication history: Received on 25 August 2025; revised on 01 October 2025; accepted on 03 October 2025

Article DOI: <https://doi.org/10.30574/msabp.2025.16.1.0064>

Abstract

Background: Otomycosis is a superficial fungal infection of the ear canal which requires prolonged treatment for patients and clinicians. Objectives: The aim of this study was to compare the clinical aspects of Clotrimazole 1% cream with Natamycin 5% drops in the treatment of otomycosis.

Methods: This research used an unpaired numerical comparative analytic study with a parallel trial design. The study sample consisted of 30 patients with otomycosis, divided into two therapy groups; Clotrimazole cream and Natamycin drops. Clinical symptoms (pain, itching and ear fullness) and clinical signs (ear canal condition, secretions and hyphae/spores) were evaluated on days 7 and 14. Subjects were given follow-up therapy in the form of reapplication. Statistical tests were used, including the Mann-Whitney test and Fisher's Exact test.

Results: No significant differences were observed in the median of otalgia, itching, and blockage score before and after treatment for Clotrimazole and Natamycin ($p=0.825$), ($p=0.006$), ($p=0.016$), respectively. In addition, there was a significant reduction in the number of patients reporting ear discharge ($p = 0.256$), secretions ($p = 1.0$), and hyphae/spores ($p = 1.0$).

Conclusion: There was no significant difference in the clinical outcomes between Clotrimazole cream and Natamycin drops in patients with otomycosis.

Keywords: Otomycosis; Natamycin Drops; Clotrimazole Cream; Anti-Fungal Therapy

1. Introduction

Otomycosis is a superficial fungal infection of the external auditory canal frequently encountered by otolaryngologists during routine otoscopic examinations. Although it rarely poses a life-threatening condition, otomycosis often presents therapeutic challenges. It becomes a source of frustration for both patients and clinicians, due to its prolonged treatment duration and high recurrence rate [1,2,3]. The most common fungal pathogens are *Aspergillus* spp. and *Candida* spp. However, species distribution can vary across countries such as Iran, India, China, Egypt, Mexico, and Brazil. A literature review by Bojanovic M et al. confirmed that *Aspergillus* and *Candida* remain the predominant agents, though other fungi like *Cryptococcus* spp., *Rhodotorula* spp., *Geotrichum candidum*, dermatophytes (*Trichophyton mentagrophytes*), and non-dermatophytes have also been identified. [4]. The condition is strongly associated with warm and humid climates. It is thus more prevalent in tropical and subtropical countries, including Indonesia. Despite its relatively high occurrence, to date, there are no definitive national data regarding the incidence of otomycosis in Indonesia [4,5].

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A study conducted at Prof. Dr. Margono Soekarjo General Hospital, Purwokerto, from May 2022 to January 2023, revealed that *Aspergillus niger* was the most commonly causative agent (19.56%), with the majority of cases occurring in females (55.56%), particularly within the 26–35 years age group (44.45%). The clinical presentation of otomycosis is generally non-specific, with the most commonly reported symptoms being pruritus (91%), otorrhea (71%), otalgia (65%), a sensation of ear fullness (54%), hearing loss (38%), and tinnitus (32%). Several challenges remain in the management of otomycosis, including antifungal resistance, concerns about drug safety, local mucosal irritation, and the lack of standardised treatment duration. These challenges have prompted further research to compare the clinical effectiveness of topical 1% Clotrimazole cream and 5% Natamycin ear drops in the treatment of otomycosis [6].

2. Materials and methods

This research was designed as a non-paired, numerical comparative analytical study with a parallel trial design. The study was conducted at the Otorhinolaryngology Outpatient Clinic of Dr. Zainoel Abidin General Hospital (RSUDZA), Banda Aceh, from November 2024 to January 2025. The study sample was 30 patients with otomycosis and were divided into two treatment groups; Clotrimazole cream, and Natamycin ear drops. Clinical symptoms and signs were evaluated on days 7 and 14. The sample included otomycosis patients who received treatment at RSUDZA and met the study’s inclusion and exclusion criteria. Subjects who met the inclusion and exclusion criteria were subsequently randomized to determine their allocation into one of the study groups. The type of randomization used was block randomization with two groups, generated using a computerized system (computer-generated blocks of two). Diagnosis of otomycosis was based on history taking and physical examination.

Univariate analysis for categorical variables will be presented as frequencies and percentages. Meanwhile, numerical variables will be presented as mean and standard deviation. The collected data will be statistically analyzed to determine significance using the Independent Samples t-test. If the data are not normally distributed, as determined by the Shapiro-Wilk normality test, an alternative non-parametric test, the Mann-Whitney U test, will be used. For categorical data, the Fisher’s Exact Test will be applied. The basis for statistical decision-making in this study is the *p*-value. A *p*-value less than 0.05 indicates that the null hypothesis is rejected and the alternative hypothesis is accepted.

3. Results

The progressive decrease in otalgia, pruritus, and ear fullness scores throughout three visits indicates a clinically significant improvement in symptoms over time in both the group treated with 1% Clotrimazole cream and the group treated with 5% Natamycin ear drops.

Table 1 Comparison of VAS Scores for Clinical Symptoms Between 1% Clotrimazole Cream and 5% Natamycin Ear Drops

Clinical Symptoms	Group	Day- 0			p*	Day-7			p*	Day-14			p*
		Median	Min	Max		Median	Min	Max		Median	Min	Max	
Otalgia	Clotrimazole 1%	2.0	1.0	5.0	0.860	0.0	0.0	2.0	0.825	0.0	0.0	0.0	-
	Natamycin 5%	3.0	1.0	5.0		0.0	0.0	1.0		0.0	0.0	0.0	
Pruritus	Clotrimazole 1%	2.0	1.0	5.0	0.443	0.0	0.0	2.0	0.006	0.0	0.0	0.0	-
	Natamycin 5%	3.0	1.0	5.0		0.0	0.0	1.0		0.0	0.0	0.0	
Ear Fullness	Clotrimazole 1%	2.0	1.0	5.0	0.013	0.0	0.0	2.0	0.016	0.0	0.0	0.0	-
	Natamycin 5%	3.0	1.0	5.0		0.0	0.0	1.0		0.0	0.0	0.0	

*Mann-Whitney Test

Table 1 showed that at baseline (day 0), the median VAS score for otalgia was similar between the two groups: 2.0 in the Clotrimazole group and 3.0 in the Natamycin group, with a *p*-value of 0.860, indicating no statistically significant difference. On day 7 and day 14, both groups demonstrated a reduction in VAS scores to a median of 0.0, suggesting

clinical resolution of otalgia in the majority of patients. The p-value on day 7 remained non-significant ($p = 0.825$), indicating comparable effectiveness between Clotrimazole and Natamycin in relieving otalgia.

For pruritus, the initial median VAS score on day 0 was 2.0 for Clotrimazole and 3.0 for Natamycin ($p = 0.443$), with no significant difference. On day 7, the median score in the Clotrimazole group remained 0.0 but ranged up to 2.0, while the Natamycin group showed a median and maximum of 1.0. The p-value of 0.006 indicated a statistically significant difference, with Natamycin demonstrating faster improvement in pruritus. By day 14, both groups achieved complete resolution, with a median VAS score of 0.0 and a range of 0.0. No further statistical comparison was performed.

Regarding the ear fullness symptom, the median VAS score on day 0 was 2.0 for Clotrimazole and 3.0 for Natamycin, with a statistically significant difference ($p = 0.013$). By day 7, the Clotrimazole group maintained a median of 0.0 with a maximum of 2.0. In contrast, the Natamycin group showed a maximum of only 1.0 ($p = 0.016$), indicating superior efficacy of Natamycin in relieving the sensation of ear fullness. By day 14, both groups reached full clinical resolution (median and range 0.0), with no residual clinical or statistical differences observed.

Table 2 showed that on day 0, the majority of patients in both treatment groups presented with edematous ear canals, with 80% in the Clotrimazole group and 93.3% in the Natamycin group. The proportion of patients with a patent (clear) ear canal remained very low, at 13.3% in the Clotrimazole group and 6.7% in the Natamycin group. There was no statistically significant difference between the two groups ($p = 0.598$). By day 7, clinical improvement began to emerge, marked by an increased number of patients with patent ear canals and a reduction in oedema and hyperemia. Although there was a clinical tendency toward better outcomes in the Natamycin group, the difference was not statistically significant ($p = 0.256$).

Table 2 Comparison of Ear Canal Condition Based on the Administration of 1% Clotrimazole Cream and 5% Natamycin Drops

Clinical Signs	Group	Clear Ear Canal		Hiperemis		Edematous		Total		p*
		n	%	n	%	n	%	n	%	
Ear Canal Day-0	Clotrimazole 1%	2	13.3	1	6.7	12	80.0	15	100	0.598
	Natamycin 5%	1	6.7	0	0.0	14	93.3	15	100	
	Total	3	10.0	1	3.3	26	86.7	30	100	
Ear Canal Day-7	Clotrimazole 1%	10	66.7	2	13.3	3	20.0	15	100	0.256
	Natamycin 5%	12	80	3	20.0	0	0.0	15	100	
	Total	22	73.3	5	16.7	3	10.0	30	100	
Ear Canal Day-14	Clotrimazole 1%	15	100	0	0.0	0	0.0	15	100	-
	Natamycin 5%	15	100	0	0.0	0	0.0	15	100	
	Total	30	100	0	0.0	0	0.0	30	100	

*Fisher Extract Test

By day 14, all patients (100%) in both groups had clear ear canals, free from signs of hyperemia or oedema. These results indicate that both treatments were equally effective in restoring normal ear canal conditions by the end of the observation period.

Table 3 Comparison of Ear Canal Discharge Between 1% Clotrimazole Cream and Natamycin 5% Drops

Clinical Signs	Group	Absent		Present		Total		p*
		n	%	n	%	n	%	
Ear Canal Discharge Day-0	Clotrimazole 1%	8	53.3	7	46.7	15	100	0.109
	Natamycin 5%	13	86.7	2	13.3	15	100	
	Total	21	70	9	30	30	100	
Ear Canal Discharge Day-7	Clotrimazole 1%	14	93.3	1	6.7	15	100	1.000
	Natamycin 5%	15	100	0	0.0	15	100	
	Total	29	96.7	1	3.3	30	100	
Ear Canal Discharge Day-14	Clotrimazole 1%	15	100	0	0.0	15	100	-
	Natamycin 5%	15	100	0	0.0	15	100	
	Total	30	100	0	0.0	30	100	

* Fisher Extract Test

Table 3 showed that on day 0, the proportion of patients experiencing ear canal discharge was relatively high. Specifically, 46.7% of patients in the Clotrimazole 1% cream group still had discharge, while only 13.3% in the Natamycin group exhibited the same issue. A significant majority of patients in the Natamycin group (86.7%) showed no discharge at baseline, compared to 53.3% in the Clotrimazole group. However, the difference between the two groups was not statistically significant ($p = 0.109$), even though there was a clinical trend indicating that improvement occurred earlier in the Natamycin group. By day 7, a marked improvement was observed in both groups: 93.3% of patients in the Clotrimazole group and 100% of patients in the Natamycin group were free of ear discharge. On day 14, all patients (100%) in both treatment groups showed complete resolution of discharge in the ear canal.

Table 4 Comparison of Clinical Signs of Hyphae/Spores in the Ear Canal Between 1% Clotrimazole Cream and Natamycin 5% Drops

Clinical Signs	Group	Absent		Present		Total		p*
		n	%	n	%	n	%	
Hyphae/Spores Day-0	Clotrimazole 1%	0	0.0	15	100.0	15	100.0	-
	Natamycin 5%	0	0.0	15	100.0	15	100.0	
	Total	0	0.0	30	100.0	30	100.0	
Hyphae/Spores Day-7	Clotrimazole 1%	13	86.7	2	13.3	15	100.0	1.000
	Natamycin 5%	13	86.7	2	13.3	15	100.0	
	Total	26	86.7	4	13.3	30	100.0	
Hyphae/Spores Day-14	Clotrimazole 1%	15	100.0	0	0.0	15	100.0	-
	Natamycin 5%	15	100.0	0	0.0	15	100.0	
	Total	30	100.0	0	0.0	30	100.0	

* Fisher Extract Test

Table 4 showed that on day 0, all patients (100%) in both treatment groups were positive for hyphae/spores in the ear canal. By day 7, only two patients (13.3%) in each group still showed the presence of hyphae/spores. There was no statistically significant difference between the two groups ($p = 1.000$), indicating comparable effectiveness in fungal eradication by day 7. On day 14, all patients (100%) in both groups tested negative for hyphae/spores, indicating complete fungal eradication.

4. Discussion

The clinical symptoms experienced by patients can be assessed using various pain measurement scales, one of which is the Visual Analogue Scale (VAS). VAS is a simple and easy-to-use tool for evaluating the intensity of symptoms such as pain or discomfort [7]. Clotrimazole, an antifungal agent from the azole group, has a broad spectrum of activity and is effective against various fungal species, including *Aspergillus* and *Candida*. In several previous studies, Clotrimazole demonstrated significant zones of inhibition against most fungal strains tested, confirming its effectiveness in the treatment of otomycosis. In addition to its antifungal activity, Clotrimazole also exhibits antibacterial effects against gram-positive bacteria such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, which may provide additional benefits in treating mixed ear infections [2,8]. A study reported that Natamycin therapy could eliminate symptoms more rapidly, particularly in cases of otomycosis caused by *Aspergillus* spp. It can be concluded that both Clotrimazole and Natamycin have comparable effectiveness in reducing ear pain due to otomycosis, with no significant difference between them [9].

Patients reported a reduction in ear itching after administering 1% Clotrimazole cream. Itching is a common and prominent symptom in individuals with otomycosis, often caused by an irritative and inflammatory response due to fungal proliferation in the external auditory canal. This process stimulates sensory nerve endings in the skin, resulting in an itching sensation. Furthermore, particular fungal species produce metabolites or toxins that can further irritate the skin, exacerbating the itching in the infected area. Disruption of the skin barrier, such as desquamation or superficial ulceration caused by fungal infection, may also trigger the activation of itch receptors [10,11,12].

Itching remains the most frequently reported symptom among patients with otomycosis. A study by Zulhaidah *et al*, found that 76.8% of otomycosis patients experienced ear pruritus. Additionally, a 2022 study by Nemati *et al.*, which compared the effectiveness of several antifungal agents (Clotrimazole, Sertaconazole, and Miconazole), showed that significant improvement in symptoms—particularly itching—was only observed after one week of Clotrimazole cream use [13].

Following the administration of 5% Natamycin ear drops, a reduction in pruritus was also observed, as reflected by the decrease in VAS scores from the initial visit to day 14. Natamycin, a polyene-class antifungal agent, is effective against various pathogenic fungi. To date, no previous studies have specifically reported the reduction of pruritic symptoms following the use of 5% Natamycin. The itching sensation is most likely caused by inflammation or epithelial damage in the external auditory canal [14]. However, a statistically significant difference was observed at the follow-up visit ($p = 0.006$), indicating that Natamycin provided faster relief from pruritus compared to Clotrimazole. A separate study comparing a single dose of Clotrimazole in cream form with ear drops for the treatment of otomycosis showed equivalent efficacy in relieving pruritic symptoms [15].

Regarding the sensation of ear fullness, the analysis revealed that the median VAS scores for both the Clotrimazole and Natamycin groups did not differ significantly on days 0 and 7. This suggests that there was an initial disparity in patient condition between the two groups, making it difficult to draw a definitive conclusion regarding the relative effectiveness of the two therapies for this symptom. Nonetheless, Natamycin appeared to produce a greater reduction in the median score compared to Clotrimazole. These findings are supported by a study by Al-Karawi *et al*, which found that patients treated with 1% Clotrimazole cream were more likely to experience a sensation of ear fullness [16]. Cream formulations are more often associated with a feeling of ear blockage during the first seven days of treatment compared to ear drops [15].

On clinical examination of the ear canal, the majority of patients on day 0 presented with narrowed ear canals due to oedema. The incidence of oedema was higher in the Natamycin group (93.3%) compared to the Clotrimazole group (80%), although Fisher's Exact test showed no statistically significant difference between the treatment groups ($p = 0.598$). Despite the lack of statistical significance ($p = 0.256$), Natamycin appeared to elicit a faster clinical response in reducing oedema and opening the ear canal. Research on the effectiveness of Natamycin as a treatment for otomycosis remains limited; however, Kurnatowski and Filipiak reported a clinical improvement rate of 89.4% within three weeks among patients with otomycosis treated with Natamycin [4].

In terms of ear canal secretions, analysis showed a higher secretion rate in the Clotrimazole group (46.7%) compared to the Natamycin group (13.3%) on day 0. However, this difference was not statistically significant ($p = 0.109$). A study by Navaneethan *et al*, in India comparing Clotrimazole drops, Miconazole cream, and Fluconazole drops found that all three antifungal agents had equivalent efficacy in resolving otorrhea [17].

Regarding the presence of hyphae/spores in the ear canal, all patients (100%) in both treatment groups had visible fungal elements on day 0, indicating active fungal infection. By day 7, 86.7% of patients were free of hyphae/spores, while 13.3% still showed signs of ongoing infection. At the final visit, all patients (100%) were negative for fungal elements, suggesting that both 1% Clotrimazole cream and 5% Natamycin ear drops were equally effective in eradicating fungal infections. A study by Mishra *et al*, which compared antifungal agents in drop and cream formulations, reported that after two weeks of treatment, nine patients in the drops group and eleven patients in the cream group still demonstrated fungal hyphae, with no statistically significant difference in the presence of fungal structures between the two treatment groups [15].

5. Conclusions

There was no statistically significant difference in the effectiveness of Natamycin and Clotrimazole for reducing clinical symptoms of otomycosis. Both treatments showed favorable recovery outcomes without any serious adverse effects.

Compliance with ethical standards

Acknowledgments

We would like to express our sincere to all the study participants who granted their consent to be enrolled. The authors also appreciate and thank to Otorhinolaryngology-Head and Neck Department for helping this study.

Disclosure of conflict of interest

The authors have declared that no competing interests exist in this study.

Statement of ethical approval

The Study has been approved by the Health Research Ethics Committee of the Faculty of Medicine at Universitas Syiah Kuala with a number of ethical contributions KEPPKN registration number (Description of ethical expedited number: 279/ETIK-RSUDZA/2024).

Statement of informed consent

All authors declare that informed consent was obtained from all individual participants included in the study.

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