Original Article

Comparative evaluation of fluconazole and clotrimazole in treatment of oral candidiasis

Pragati C Madane, A Sailaja Choudary, T A Deepak, M S Abhinethra, L Upasana, Ruthvik Balaji

Department of Oral Medicine and Radiology, V.S Dental College and Hospital, Bengaluru, Karnataka, India

Abstract

Context: Oral candidiasis is the most common opportunistic infection affecting the oral mucosa. Most commonly, the lesions are caused by *Candida albicans* and other organisms isolated are *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida dubliniensis*. As an opportunistic infection, it is seen affecting the young, old and debilitating people. This infection is seen to be enervative, exhausting and crippling; a few routinely employed antifungal agents are used in our study.

Aims: We aimed to compare the clinical and mycological effectiveness of topical fluconazole and clotrimazole in the treatment of oral candidiasis.

Settings and Design: A total of 40 subjects were taken and randomly divided into two groups of 20 each. Group 1 included patients treated with topical clotrimazole and Group 2 included patients treated with topical fluconazole.

Subjects and Methods: Patients were graded according to severity, and swab was taken for species identification and colony count. Patients were treated with clotrimazole and fluconazole according to their group they were also assessed post treatment for clinical signs and colony count changes.

Statistical Analysis Used: Data were analyzed using the statistical package SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and the level of significance was set at $P < 0.05$. Descriptive statistics was performed to assess the mean and standard deviation of the respective groups.

Results: The clinical resolution rate of 80% and 100% was noted in the clotrimazole and fluconazole groups, respectively. The mycological cure rate of 82.52% and 86.38% was noted in the clotrimazole and fluconazole groups, respectively. Statistically significant results were obtained in clinical resolution rates and no significant results were obtained when mycological cure rates were compared.

Conclusions: We conclude that the clinical cure rate of fluconazole is slightly better than clotrimazole while mycological cure rate was approximately similar.

Keywords: Clotrimazole, fluconazole, oral candidiasis

Address for correspondence: Dr. Pragati C Madane, MDS (OMR), V. S Dental College and Hospital, VV Puram, Basavanagudi, Bengaluru- 560 004, Karnataka, India.
E-mail: pragaticmadane@yahoo.com

Submitted: 01-Aug-2021, **Accepted:** 27-Dec-2021, **Published:** 22-Dec-2022

INTRODUCTION

Among the fungal infections affecting the oral cavity, candidiasis is the most common disease. The microorganism causing candidiasis belongs to the genus *Candida*.[1] They are fungal eukaryotic microorganisms. They are characterized

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/jomfp.jomfp_266_21

How to cite this article: Madane PC, Choudary AS, Deepak TA, Abhinethra MS, Upasana L, Balaji R. Comparative evaluation of fluconazole and clotrimazole in treatment of oral candidiasis. J Oral Maxillofac Pathol 2022;26:595-6.

as including white asporogenous (imperfect) yeasts capable of forming pseudohyphae. There are seven *Candida* species of major medical importance.[2] By far, the most important of these is *Candida albicans* which is isolated most frequently (over 80%) and believed to be more virulent in humans. The other *Candida* spp. encountered in human infections are *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida stellatoidea*, *Candida krusei* and *Candida kyfer*.[1]

In healthy individuals, immune system and normal microbial flora inhibit the growth of *Candida*. When immunity is disrupted, it could be because of local cause, use of corticosteroids or immunosuppression in any other form leads to the disease. The yeasts' penetration of the epithelial cells is facilitated by their production of lipases, and for the yeasts to remain within the epithelium, they must overcome constant desquamation of surface epithelial cells.[3]

C. albicans is a normal commensal and is present in 75% of the population. Virulence of *C. albicans* relies on two likely complementary mechanisms: induced endocytosis mediated by Als3 and Ssa1 and active penetration mediated by yet undefined molecular mechanisms. *C. glabrata* is the second or third causative agent of superficial (oral, esophageal, vaginal or urinary) or systemic candidal infections, which are often nosocomial. Its virulence is attributed to its adherence to the epithelial and the endothelial cells which has been associated with the cell surface hydrophobicity of the fungi, enabling it to interact with the adhesin receptors on the host cells. *C. krusei* is the fifth most common cause of candidemia, it is most noteworthy for its innate resistance to the antifungal agent fluconazole in addition to somewhat reduced susceptibility to other drugs. *C. tropicalis* has been observed to be the most common cause of invasive candidiasis in neutropenic patients such as those with acute leukemia or those who have undergone bone marrow transplantation.

Fluconazole is a triazole belonging to an azole group of antifungals.[4] It is well established as a first-line management option for both localized and systemic *C. albicans* infections. It is used as a systemic antifungal drug as there was no topical preparations available. With the advent of topical fluconazole gel, it underscores the need for studies on its efficacy on oral candidiasis.

Clotrimazole is an imidazole belonging to an azole group of antifungals.[4] It is the first drug of choice for the treatment of oral candidiasis. Not much research has been done on finding an alternative topical drug.

Hence, this study was an attempt to evaluate and compare the clinical and mycological effectiveness of topical fluconazole and topical clotrimazole in the treatment of oral candidiasis.

SUBJECTS AND METHODS

This study was conducted on the patients reporting to the Department of Oral Medicine and Radiology, V.S. Dental College and Hospital, Bengaluru, diagnosed with oral candidiasis. This study was approved by the institutional ethical board, and all the patients read and signed informed consent.

A total of 40 subjects diagnosed with oral candidiasis were randomly divided into two groups, 20 in each. All the subjects were older than 18 years. The inclusion criteria were as follows: white, scrapable, pseudomembranous, erythematous lesions and laboratory-confirmed cases of oral candidiasis. The exclusion criteria were as follows: (1) patients with systemic candidiasis, (2) patients with HIV, (3) patients undergoing chemotherapy, (4) patients with known drug allergy to fluconazole and clotrimazole and (5) patients with chronic plaque type and nodular candidiasis (candidal leukoplakia).

Patients were clinically examined for oral lesions. White, scrapable, pseudomembranous, erythematous lesions were included in the study.

The clinical signs were categorized into mild (+), moderate (++) and severe (+++) based on the extent of the lesion in the oral cavity. It was considered as "mild" if it involved one or two localized areas, "moderate" if it involved more than two localized areas and "severe" if there was a generalized involvement.

Swab was taken from the infected area and subjected to Gram's stain and culture on Sabouraud dextrose agar medium and incubated at 37°C for 48 h. Colony count and species identification was done. Based on the culture report, candidiasis was confirmed. Commercially available clotrimazole 1% gel and fluconazole 0.5% gel were used.

Patients were then randomly divided into two groups: Group 1: patients of Group 1 were given clotrimazole 1% gel. Patients were advised to apply on the lesion 3 times daily for 15 days.

Group 2: Patients of Group 2 were given fluconazole 0.5% gel. Patients were advised to apply on the lesion 3 times daily for 15 days. Patients were recalled on the 18th day.

Clinical examination and swab culture test were repeated 48 h after stoppage of medication.

Patients were clinically examined for oral lesions. The presence or absence of lesion was noted and graded. Swab was taken from the same infected region and subjected for culture. The presence or absence of *Candida* and colony count and speciation was done. Comparison between the effectiveness of topical fluconazole gel and topical clotrimazole gel for the treatment of oral candidiasis was performed.

Statistical analysis

Data were analyzed using the statistical package SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and the level of significance was set at $P < 0.05$. Descriptive statistics was performed to assess the mean and standard deviation (SD) of the respective groups. Normality of the data was assessed using Shapiro-Wilk test. Inferential statistics to find out the difference between the groups was done using Student *t*-test and Wilcoxon signed-rank test. Chi-square test was used to test the proportion between the groups.

RESULTS

Out of 20 subjects in Group I, 17 showed mild signs and 3 showed moderate signs. Out of 20 in Group II, 19 showed mild signs and 1 showed moderate signs before treatment. Clinical signs before treatment were statistically not significant [Table 1]. After treatment, 16 showed no signs and 4 showed mild signs in Group I and all 20 patients showed no signs. Clinical signs after treatment were statistically significant after treatment [Table 2].

The mean and SD candidal colony counts before and after treatment for Group I and Group II were 1545 ± 664.46, 270 ± 555.45 and 1175 ± 494.14, 160 ± 493.53, respectively [Table 3]. The *P* value for before and after treatment was 0.052 and 0.511, respectively, and it was not statistically significant.

The mean and SD candidal colony counts before and after treatment within Group I were 1545 ± 664.46 and 270 ± 555.45, respectively. The *P* value was 0.0001 and it was statistically significant [Table 4].

The mean and SD candidal colony counts before and after treatment within Group I were 1175 ± 494.14 and 160 ± 493.53, respectively. The *P* value was 0.0001 and it was statistically significant [Table 4].

Out of 20 in Group I, 19 had *C. albicans* isolates and 1 had *C. glabrata* with *C. albicans*. Out of 20 in Group II, 18 had *C. albicans* isolates, 1 had *C. glabrata* with *C. albicans* and another had *C. krusei* with *C. albicans* [Table 5].

DISCUSSION

Candida is common, harmless dimorphic yeast that lives in the oral cavity without initiating the disease until the host immunity gets compromised. *Candida* is a normal commensal and exists in the oral cavity of around 68% of the normal individuals without causing any disease. Hence, McCarthy described candidiasis as a "disease of the diseased."[5] Localized oral candidiasis is initially treated with the use of topical antifungal medication before the use of systemic antifungal drugs. Since a few decades, polyene antibiotics have been used as a drug of choice for fungal infections. However, the recent development of an azole group of drugs such as ketoconazole and fluconazole displayed potent antifungal activities when used systemically. The antifungal activity of fluconazole on topical application to treat oral candidiasis and its

Table 1: Clinical signs before treatment

	Clotrimazole (%)	Fluconazole (%)	χ^2	*P*
Mild	17 (85)	19 (95)	1.11	0.29
Moderate	3 (15)	1 (5)		

*$P<0.05$ is statistically significant

Table 2: Clinical signs after treatment

	Clotrimazole (%)	Fluconazole (%)	χ^2	*P*
No signs	16 (80)	20 (100)	4.44	0.03*
Mild	4 (20)	0		

*$P<0.05$ is statistically significant

Table 3: Examination of colony count (Wilcoxon signed-rank test) – between-group analysis

	Clotrimazole	Fluconazole
Before	1545±664.46	1175±494.14
After	270±555.45	160±493.53
Z	−3.919	−3.919
P	<0.0001*	<0.0001*
Percentage difference	82.52	86.38

*$P<0.05$ is statistically significant

Table 4: Examination of colony count (Wilcoxon signed-rank test) – within-group analysis

	Clotrimazole	Fluconazole	*Z*	*P*
Before	1545±664.46	1175±494.14	1.99	0.052
After	270±555.45	160±493.53	0.662	0.511

*$P<0.05$ is statistically significant

Table 5: Fungal species

	Clotrimazole	Fluconazole	χ^2	*P*
C. albicans	19 (95%)	18 (90%)	5.135	0.07
C. albicans + *C. glabrata*	1 (5%)	1 (5%)		
C. albicans + *C. krusei*	0	1 (5%)		

*$P<0.05$ is statistically significant. *C. albicans: Candida albicans, C. glabrata: Candida glabrata, C. krusei: Candida krusei*

comparison with the topical antifungal activity with gold standard clotrimazole drug was the principal purpose of the present study.

By considering the half-life of fluconazole and clotrimazole, clinical examination and swab collection were obtained after 48 h of use of medication to avoid recent drug effect on collected swab.[6] Swab from the same infected area was collected in the follow-up so as to maintain the standardization.

Although, oral candidiasis occurs equally in males and females of extreme ages. A study directed in 2006 displayed the incidence of the highest candida carriers, 67.4%, in the age group of 70–79 years. Oral candidiasis was present in 20% with the tendency to intensify with age (33.3% of adults aged >80 years), and the use of prosthesis was also associated with a greater colonization rate.[7] In the present study, majority of the male patients over 60 years of age groups were included. An age-related increase in oral candidiasis has been reported because of the physiological changes in the oral mucosa associated with age, such as the thinning of the mucosa, changes in the oral biochemical microenvironment and decrease in salivary flow, which could contribute to *Candida* colonization.[8,9] A similar relation was reported by Dar-Odeh and Shehabi and Loster *et al*.,[10,11] but in other studies, the results were the opposite.[11-14] Similarly, a study in 2016 interpreting the role of hyposalivation and autoimmunity in oral candidiasis reported that females had a lower risk of developing oral candidiasis than males,[15] which is in line with the present research.

In this study, the majority of the patients suffering from denture stomatitis had a greater association with *C. albicans* (92.5%). A quantifiable occurrence of *Candida* has been found to be allied with denture stomatitis disease manifestation.[16,17] Budtz-Jorgensen and Bertram described a significant relation between inflammation and *Candida* colonization in patients with denture stomatitis,[18] and this association has been confirmed in subsequent studies.[19-24] The possible etiological role in denture stomatitis occurs in combination with other factors, especially poor denture hygiene and continuous wearing of dentures. This provides a favorable environment for the fungi to grow.[10,16]

In the current study, the percentage reduction of CFUs of fungi (cure rates) in the fluconazole and clotrimazole groups was found to be 86.38 and 82.52%, respectively. Whereas, O-Prasertsawat *et al*. comparatively evaluated the effectiveness of fluconazole and clotrimazole in the treatment of vulvovaginal candidiasis, and they observed approximately 79% and 80% mycological cure rates among fluconazole and clotrimazole medications, respectively, which is in parallel with the present study.[25,26] Both the medications displayed a significant reduction in fungal growth in 15 days, and equivalent results were obtained by Sholapurkar *et al*.[5,25] Although, fluconazole displayed an enhanced cure rate when compared with clotrimazole; data did not exhibit a statistically significant difference between them. Most of the researches demonstrate related results.[5,25,27]

The present study statistics on microbiological part indicates that both fluconazole and clotrimazole were equally effective in reduction of oral candidal infection when applied topically. This result is related to some of the other study results.[5,25,28]

The statistics on clinical signs and symptoms clearly denotes a significantly higher reduction of clinical signs among the fluconazole group when compared to the clotrimazole group. This indicates that fluconazole is a better medication when compared to clotrimazole when applied topically to reduce the clinical signs. However, contradicting to the present study result, a comparative study aiming to check the efficacy of clotrimazole, fluconazole and itraconazole in vaginal candidiasis reported that the overall mycological cure rates of itraconazole or clotrimazole are more effective than fluconazole in the treatment of acute vaginal candidiasis.[29]

There were some limitations in this study. It was a single-center study with small number of sample. Secondly, it was not double-blinded, which might have led to some observer or selection bias. Thirdly, patients were not followed up after 2 weeks for any probability of reappearance, and finally, the present study did not focus on underlying etiologic factors for the occurrence of candidiasis.

CONCLUSION

Fluconazole gel displayed a greater efficacy when compared to clotrimazole when used topically for the treatment of oral candidiasis. Further studies should be held in the same field with a larger sample size to generalize the result.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. McCullough MJ, Savage NW. Oral candidosis and the therapeutic use of antifungal agents in dentistry. Aust Dent J 2005;50:S36-9.
2. Patton LL, Bonito AJ, Shugars DA, Chapel Hill NC. A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001;92:170-9.
3. Jontell M, Holmstrup P. Red and white lesions of the oral mucosa. In: Glick M, editor. Burket's Oral Medicine. 12th ed. Shelton: People's Medical Publishing House-USA; 2015. p. 91-121.
4. Tripathi KD. Essentials of Medical Pharmacology. 6th edition. New Delhi: JP Medical Ltd; 2008. p. 757.
5. Sholapurkar AA, Pai KM, Rao S. Comparison of efficacy of fluconazole mouthrinse and clotrimazole mouthpaint in the treatment of oral candidiasis. Aust Dent J 2009;54:341-6.
6. García-Valcárcel AI, Tadeo JL. Influence of moisture on the availability and persistence of clotrimazole and fluconazole in sludge-amended soil. Environ Toxicol Chem 2012;31:501-7.
7. Blignaut E, Pujol C, Lockhart S, Joly S, Soll DR. Ca3 fingerprinting of *Candida albicans* isolates from human immunodeficiency virus-positive and healthy individuals reveals a new clade in South Africa. J Clin Microbiol 2002;40:826-36.
8. Patel PN, Sah P, Chandrashekar C, Vidyasagar S, Venkata Rao J, Tiwari M, *et al.* Oral candidal speciation, virulence and antifungal susceptibility in type 2 diabetes mellitus. Diabetes Res Clin Pract 2017;125:10-9.
9. Benito-Cruz B, Aranda-Romo S, López-Esqueda FJ, de la Rosa-García E, Rosas-Hernández R, Sánchez-Vargas LO. Oral Candida isolates and fluconazole susceptibility patterns in older Mexican women. Arch Gerontol Geriatr 2016;65:204-10.
10. Dar-Odeh NS, Shehabi AA. Oral candidosis in patients with removable dentures. Mycoses 2003;46:187-91.
11. Loster JE, Wieczorek A, Loster BW. Correlation between age and gender in *Candida* species infections of complete denture wearers: A retrospective analysis. Clin Interv Aging 2016;11:1707-14.
12. Jainkittivong A, Aneksuk V, Langlais RP. Oral mucosal lesions in denture wearers. Gerodontology 2010;27:26-32.
13. Abaci O, Haliki-Uztan A, Ozturk B, Toksavul S, Ulusoy M, Boyacioglu H. Determining *Candida* spp. incidence in denture wearers. Mycopathologia 2010;169:365-72.
14. Figueiral MH, Azul A, Pinto E, Fonseca P, Branco FM, Scully CJ. Denture-related stomatitis: Identification of aetiological and predisposing factors – A large cohort. J Oral Rehabil 2007;34:448-55.
15. Billings M, Dye BA, Iafolla T, Grisius M, Alevizos I. Elucidating the role of hyposalivation and autoimmunity in oral candidiasis. Oral Dis 2017;23:387-94.
16. Gendreau L, Loewy ZG. Epidemiology and etiology of denture stomatitis. J Prosthodont 2011;20:251-60.
17. Webb BC, Thomas CJ, Willcox MD, Harty DW, Knox KW. Candida-associated denture stomatitis. Aetiology and management: A review: Part 1. Factors influencing distribution of candida species in the oral cavity. Aust Dent J 1998;43:45-50.
18. Budtz-Jorgensen E, Bertram U. Denture stomatitis. I. The etiology in relation to trauma and infection. Acta Odontol Scand 1970;28:71-92.
19. Kulak-Ozkan Y, Kazazoglu E, Arikan A. Oral hygiene habits, denture cleanliness, presence of yeasts and stomatitis in elderly people. J Oral Rehabil 2002;29:300-4.
20. Baena-Monroy T, Moreno-Maldonado V, Franco-Martínez F, Aldape-Barrios B, Quindós G, Sánchez-Vargas LO. *Candida albicans*, *Staphylococcus aureus* and *Streptococcus mutans* colonization in patients wearing dental prosthesis. Med Oral Patol Oral Cir Bucal 2005;10 Suppl 1:E27-39.
21. Coco BJ, Bagg J, Cross LJ, Jose A, Cross J, Ramage G. Mixed *Candida albicans* and *Candida glabrata* populations associated with the pathogenesis of denture stomatitis. Oral Microbiol Immunol 2008;23:377-83.
22. Dağistan S, Aktas AE, Caglayan F, Ayyildiz A, Bilge M. Differential diagnosis of denture-induced stomatitis, *Candida*, and their variations in patients using complete denture: A clinical and mycological study. Mycoses 2009;52:266-71.
23. Kulak Y, Arikan A. Aetiology of denture stomatitis. J Marmara Univ Dent Fac 1993;1:307-14.
24. Nanetti A, Stancari F, Ferri M, Mazzoni A. Relationship between *Candida albicans* and denture stomatitis: A clinical and microbiological study. New Microbiol 1993;16:287-91.
25. Reddy RCJ, Jeelani S, Duraiselvi P, Kandasamy M, Kumar GS, Pandian RA. Assessment of Effectiveness of fluconazole and clotrimazole in treating oral candidiasis patients: A comparative study. J Int Soc Prev Community Dent 2017;7:90-4.
26. O-Prasertsawat P, Bourlert A. Comparative study of fluconazole and clotrimazole for the treatment of vulvovaginal candidiasis. Sex Transm Dis 1995;22:228-30.
27. Banerjee M, Ghosh AK, Basak S, Das KD, Gangopadhyay N. Comparative evaluation of efficacy and safety of topical fluconazole and clotrimazole in the treatment of tinea corporis. Journal of Pakistan Association of Dermatologists 2012;22(4).
28. Koletar SL, Russell JA, Fass RJ, Plouffe JF. Comparison of oral fluconazole and clotrimazole troches as treatment for oral candidiasis in patients infected with human immunodeficiency virus. Antimicrob Agents Chemother 1990;34:2267-8.
29. Woolley PD, Higgins SP. Comparison of clotrimazole, fluconazole and itraconazole in vaginal candidiasis. Br J Clin Pract 1995;49:65-6.