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ORIGINAL ARTICLE

Comparison of Efficacy of Ketoconazole and Fluconazole Incorporated into Tissue Conditioner for the Treatment of Denture Stomatitis

Mamta Sharma[1], Aditi Sharma[2], Asra Tabassum[3]

[1]Dental surgeon, Department of Oral Medicine and Radiology, [2]Lecturer, [3]House Surgeon Department of Prosthodontics, Indira Gandhi Govt Dental Hospital Jammu, India

***ABSTRACT*:**
Background: The implementation of topical antifungal therapy is difficult in geriatric patients due to multiple factors like cognitive impairment, reduced motor activity and memory loss. In addition to this maintenance of an effective topical antifungal dose in the oral cavity is difficult. These agents do not adhere and remain in contact with oral mucosa due to regular and constant wash out by the salivary flow. **Aim of the study:** To compare efficacy of Ketoconazole and Fluconazole incorporated into Tissue Conditioner for the treatment of denture stomatitis. **Materials and methods:** The present study was conducted in the Department of Prosthodontics of the Dental institution. For the study sample, we obtained clinical isolates of Candida albicans, from the Department of molecular microbiology of medical institute, to use as test organisms for the current experimental study. Tissue conditioner was mixed and prepared according to manufacturer's instruction. Antifungal agents, ketoconazole and fluconazole were mixed into tissue conditioner powder at concentrations of 5% wt/wt in a sterile plate. **Results:** We observed that that Ketaconazole solution was the most efficient for inhibiting attachment and colonization of C. albicans. Fluconazole solution is partially effective efficient for inhibiting attachment and colonization of C. albicans. **Conclusion:** The incorporation of ketoconazole or fluconazole into the tissue conditioners is effective in treatment of chronic atrophic candidiasis in denture users; however, ketoconazole was found to be more effective as compared to fluconazole.
Key words: Ketoconazole, Fluconazole, tissue conditioner, denture stomatitis.

Corresponding Author: Dr. Mamta Sharma, Dental surgeon, Department of Oral Medicine and Radiology, Indira Gandhi Govt Dental Hospital Jammu, India

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INTRODUCTION:

The Candida-associated denture stomatitis is a common condition characterized by generalized inflammation of the palatal mucosa covered by the denture. It is a harmless form of oral candidiasis and is associated with a quantitative increase of yeasts on the mucosa and the denture's fit surface.[1,2] Usually a mixture of Candida species such as Candida albicans, Candida tropicals, Candida krusei, Candida guilliermondii, Candida parapsilosis, Candida glabrata can be isolated from oral candidal lesions. Candida albicans, however, has been claimed to be the principal pathogen that has a main role in the development of oral candidosis.[3]The presence of numerous yeasts may give rise to spreading to the angles of the mouth, the tongue, the pharynx, and the alimentary and respiratory tracts. The lesion may heal partially after topical antifungal treatment but the incidence of relapse is, however, very high.[4, 5] Tissue conditioners are soft, resilient, temporary relining materials which by reducing and evenly distributing stresses on the mucosa of the basal seat, have a rehabilitating effect on unhealthy tissue and allow the condition to return to normal health. The implementation of topical antifungal therapy is difficult in geriatric patients due to multiple factors like cognitive impairment, reduced motor activity and memory loss. In addition to this maintenance of an effective topical antifungal dose in the oral cavity is difficult. These agents do not adhere and remain in contact with oral mucosa due to regular and constant wash out by the salivary flow. To overcome this problem antifungal agents can be incorporated in tissue conditioners to investigate their effectiveness against Candida albicans.[6-8] Hence, we planned the study to compare efficacy of Ketoconazole and Fluconazole incorporated into Tissue Conditioner for the treatment of denture stomatitis.

MATERIALS AND METHODS:

The present study was conducted in the Department of Prosthodontics of the Dental institution. The protocol of the study was approved from the ethical committee of the institute prior to starting the study. For the study sample, we obtained clinical isolates of Candida albicans, from the Department of molecular microbiology of medical institute, to use as test organisms for the current experimental study. Candida albicans was cultured onto Sabouraud dextrose agar plate and incubated at 37ºC for 2 days. A colony from the stock culture was then diluted in 2 ml sterile saline and a suspension of 1×106 CFU/ml was prepared. Tissue conditioner was mixed and prepared according to manufacturer's instruction. Antifungal agents, ketoconazole

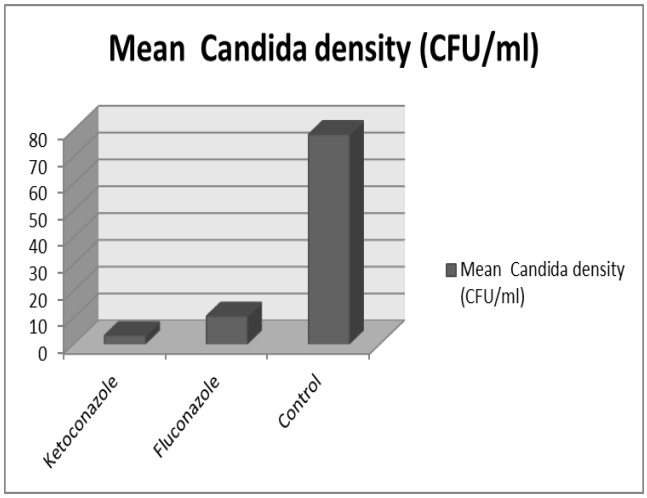
and fluconazole were mixed into tissue conditioner powder at concentrations of 5% wt/wt in a sterile plate. A sterile glass rod was used to prepare a thin film of tissue conditioner with 1mm thickness and punched as 5mm diameter disks. One specimens of pure tissue conditioner was also prepared as negative control. All disks were contaminated with 100 µl of 1 × 10 6 CFU/ml C. albicans cell suspension and the cell culture plate were incubated at 35ºC on a rotary shaker for 48 hours. The plates were incubated at 37ºC for 48 hours and the colonies were enumerated. The data was tabulated for further evaluation.
The statistical analysis of the data was done using SPSS program for windows. Student's t test and chi square test were used for checking the significance of the data. The statistical significance was predefined at $p<0.05$.

RESULTS:
Table 1 shows the mean Candida density (CFU/ml) for Ketoconazole, Fluconazole and control solution. We observed that that Ketaconazole solution was the most efficient for inhibiting attachment and colonization of C. albicans. Fluconazole solution is partially effective efficient for inhibiting attachment and colonization of C. albicans. The control solution was least effective with highest Candida density seen in control solution. The results were statistically significant ($p<0.05$)**[Fig 1].**

Table 1: Mean Candida density (CFU/ml) for Ketoconazole, Fluconazole and control solution

Specimens	Mean Candida density (CFU/ml)	p-value
Ketoconazole	3.18	0.03
Fluconazole	10.41	
Control	78.13	

Figure 1: Mean Candida density (CFU/ml) for Nystatin, Fluconazole and control solution



DISCUSSION:
Denture stomatitis is an inflammatory condition which compromises the mucosal surface beneath dentures. The aetiology of denture stomatitis is usually multifactorial which varies from trauma from ill fitting denture to poor immune system. There are evidences that denture stomatitis is an outcome of multispecies biofilms that include Candida albicans and Streptococcus mutans. Tissue conditioners are found to be more susceptible to colonisation by micro-organisms.[9]
In the present study, we observed that ketoconazole showed higher inhibitory effects than fluconazole as it almost completely inhibited the production of *C. albicans* in tissue conditioner disks, however fluconazole could partially prevent the growth and adhesion of *Candida*. The results were statistically significant. The results were compared with previous studies and results were consistent with previous studies.Falah-TaftiA et al evaluated the efficacy of the two common antifungal agents mixed with tissue conditioner against Candida albicans. Tissue conditioner disks (Acrosoft) with 5mm diameter and 1mm thickness containing different concentrations of nystatin and fluconazole (1%, 3%, 5%, 10% wt/wt) as well as disks with no antifungal agents (8 disks for each group) were prepared for experimental biofilm formation by inoculation with Candida albicans cell suspensions. The specimens were incubated in cell culture microtiter plate wells containing Sabouraud's broth in a rotator shaker at 30°C for 48 hours. Then, the specimens were rinsed and sonicated in sterile water to remove surface organisms. The attached yeasts were enumerated by inoculation of the yeast suspension on Sabouraud's agar. The data was compared using Kruskal-Wallis and Dunn's tests using prism software. P value less than 0.05 was considered significant. The 1% to 10% mixture of nystatin and tissue conditioner completely inhibited the attachment and colonization of Candida albicans, although for fluconazole only a 10% concentration caused complete inhibition. Nystatin showed a potentially higher effect in inhibition of candida attachment and colonization compared to that of fluconazole and a statistically significant difference was seen between 5% and 1% fluconazole. They concluded that the tissue conditioner with 1% to 10% nystatin or 10% fluconazole can completely inhibit the adhesion and colonization of Candida albicans. Chopde N et al determined and compare antifungal activity of two tissue conditioners combined with nystatin, miconazole and fluconazole against Candida albicans. Two tissue conditioners Viscogel and GC Soft combined with nystatin, miconazole and fluconazole were tested against Candida albicans using agar core inhibition diameter assay. Maximum inhibition was seen in the fluconazole groups followed by miconazole and the least inhibition was seen in case of nystatin group. It was concluded that tissue conditioners when mixed with antifungal agents showed satisfactory inhibition of Candida albicans.[10, 11]

Barua DR et al compared the efficacy of neem leaf extract and three other antimicrobial agents incorporated in a tissue conditioner against both Candida albicans and Streptococcus mutans. Standard strain of Candida albicans and Streptococcus mutans were inoculated into Sabouraud Dextrose broth and Mitis-Salivarius-Bacitracin broth respectively incubated at 37°C. Tissue conditioner (Viscogel) mixed with two different concentrations of ketoconazole, nystatin and chlorhexidinediacetate (5%, 10% w/w) and neem leaf extract (7.5% w/w and 15% w/w) and control group (plain tissue conditioner) were placed into punch hole (6 mm diameter) agar plate inoculated with Candida albicans and Streptococcus mutans. A total of 216 samples were prepared for both Candida albicans and Streptococcus mutans. Mean Inhibition Diameter (MID) across each punch holes were measured in millimetres at 24 hours and seven days and data were statistically analysed using Kruskal Wallis test followed by Mann-Whitney U test. Both ketoconazole and nystatin (10% w/w) showed maximum inhibition of 32 mm and mean of 31.75 followed by 15% w/w neem leaf extract with an inhibition of 21 mm and mean of 20.67 after 24 hours against Candida albicans whereas chlorhexidinedi acetate (10% w/w) showed mean of 25.67 followed by chlorhexidinedi acetate (5% w/w) and neem extract (15% w/w) which showed mean of 24.17 and 23.67 respectively against Streptococcus mutans. It was concluded that neem leaf extract exhibited considerable potential to be an efficacious antimicrobial agent against both Candida albicans and Streptococcus mutans. Chow CK et al incorporated antifungal agents into tissue conditioners to investigate the effectiveness of this method of drug delivery. Combinations of nystatin, fluconazole, itraconazole and Coe Soft, Viscogel, Fitt were tested at 1, 3, 5, 7, 9 and 11 wt/wt%, with and without sterilized saliva. 6 mm diameter cores were punched in Sabouraud plates pre-grown with standardized C. albicans. Antifungal agents plus tissue conditioner mixtures were injected into each core. Inhibition diameters were measured for 14 days. Cores with only tissue conditioners acted as negative control and showed no significant inhibition activity. Peak activity was between 65 to 89 hours; followed by a plateau. Itraconazole had greater fungicidal activity than fluconazole; while nystatin was found to have the least fungicidal activity. The most effective concentration for nearly all combinations was 5% wt/wt. Specimens with saliva showed greater antifungal activity than those without. Itraconazole altered the physical properties of Viscogel hence this combination is not recommended for clinical use. They concluded that the treatment of chronic atrophic candidiasis by incorporation of antifungal drugs into tissue conditioners is efficacious.[12,13]

CONCLUSION:

Within the limitations of present study we conclude that the incorporation of ketoconazoleor fluconazole into the tissue conditioners is effective in treatment of chronic atrophic candidiasis in denture users; however, ketoconazole was found to be more effective as compared to fluconazole.

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