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ORIGINAL ARTICLE

Fluconazole and/or hexetidine for management of oral candidiasis associated with denture-induced stomatitis

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OBJECTIVE: The aim of the present study was to compare the influence of fluconazole capsules and/or hexetidine mouthrinses for the management of oral candidiasis associated with denture stomatitis.

DESIGN RELEVANT: Sixty-one patients (ages 43–76 years, mean: 61) admitted to the Department of Oral Surgery and Medicine and diagnosed as suffering from oral candidiasis associated with denture stomatitis by microbiological examination were involved.

MATERIALS AND METHODS: Patients in group 1 (n = 21) were given only fluconazole capsules (Zolax 50 mg once a day), those in group 2 (n = 18) were given only hexetidine mouthrinses (Heksoral 0.1%, twice daily), whereas those in group 3 (n = 22) were given both fluconazole capsules and hexetidine mouthrinses for 14 days. The yeast colonies of the saliva samples were counted and calculated as the number of colony forming units per milliliter. The presence of yeasts in the lesion and denture samples were evaluated as present/absent according to their growth on cultures. *Candida albicans* was identified by means of germ tube analysis.

RESULTS: Patients in groups 1, 2 and 3 had a statistically significant decrease in the amount of *C. albicans* in saliva, lesions and dentures after treatment, when compared with pretreatment results ($P < 0.05$). *Candida albicans* counts in saliva, lesion and denture after treatment detected no statistically significant difference when the three groups were compared.

CONCLUSION: Of the three study groups, group 2, where hexetidine was the only medication prescribed, was found to be superior on account of fewer potential complications. We conclude that dentists should employ a more conservative intervention with oral mouthrinses rather than risk adverse effects and complications of systemic drugs for the management of oral candidiasis.

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Introduction

Denture stomatitis is a common form of oral candidiasis that manifests as a diffuse inflammation of the maxillary denture-bearing areas which is often (15–65% of cases) associated with angular cheilitis. At least 70% of individuals with clinical signs of denture stomatitis exhibit fungal growth, and this condition most likely results from yeast colonization of the oral mucosa, combined with bacterial colonization (Bhattacharyya *et al*, 2003). The reduction of salivary flow rate because of age or adverse effects of medication can predispose to oral candidiasis associated with denture-induced stomatitis (Chow *et al*, 1999). Candidial colonization and subsequent biofilm formation on denture materials may lead to stomatitis. Daily cleaning of dentures is important in the elimination of biofilm formation (Radford *et al*, 1999; Nikawa *et al*, 2003).

Nystatin, amphotericin-B and hexetidine are commonly used topical agents, whereas azoles such as fluconazole, itraconazole, and ketoconazole are available for systemic antifungal treatment (Ellepola and Samaranayake, 1998; Chow *et al*, 1999; Chandra *et al*, 2001; Dar-Odeh and Shehabi, 2003). As poorly fitting dentures and *Candida albicans* are the causative factors of oral candidiasis, treatment for both problems includes systemic antifungal drugs, mouthrinses with antifungal activity and denture care.

The aim of the present study was to compare the influence of fluconazole capsules and/or hexetidine mouthrinses for the management of oral candidiasis associated with denture stomatitis.

Materials and methods

Patient selection

Sixty-one patients ranging between 43 and 76 (mean 61) years of age and diagnosed with denture stomatitis were enrolled for study at the University of Istanbul (Department of Oral Surgery and Oral Medicine, Faculty of

Table 1 Pre-treatment comparison of values for three groups

	Treatment groups						
	Fluconazole		*Hexetidine*		*Fluconazole + hexetidine*		
	(n = 21)	*%*	*(n = 18)*	*%*	*(n = 22)*	*%*	*Two-tailed significance*
Gender							
Male	10	48	5	28	11	50	$\chi^2 = 2.32$*; $P = 0.31$
Female	11	52	13	72	11	50	
Total	21	100	18	100	22	100	
Systemic disease							
Absent	8	38	6	33	5	23	$\chi^2 = 1.24$; $P = 0.53$
Present	13	62	12	67	17	77	
Total	21	100	18	100	22	100	
Denture *C. albicans*							
Absent	7	33	5	28	5	23	$\chi^2 = 0.60$; $P = 0.70$
Present	14	67	13	72	17	77	
Total	21	100	18	100	22	100	
Lesion *C. albicans*							
Present	21	100	18	100	22	100	
Total	21	100	18	100	22	100	
Median	Min–max		Median	Min–max	Median	Min–max	
Saliva *C. albicans* (cfu ml^{-1}) 2000	500–6000		500	0–10 000	2500	0–10 000	$\chi^2_{k.w} = 1{,}21$; $P = 0{,}54$

*Chi-square test, K.W, Kruskal–Wallis test.

Dentistry). Selection of patients was based on positive *Candida* counts proven by culture of samples from saliva and microscopic examination of swabs from lesions and dentures. Age, gender and medical history of all patients were recorded. The patient population was randomly divided into three groups. Patients in Group 1 ($n = 21$) were given only fluconazole, in the form of Zolax capsules 50 mg (Adilna-Sanovel, Istanbul, Turkey), once daily; patients in group 2 were given only 0.1% hexitidine mouthrinses (Heksoral, Mega-Farma, Istanbul, Turkey) twice a day; whereas patients in group 3 ($n = 22$) were given both fluconazole and hexetidine during the 14 days of study.

Denture care

All patients were given instructions for denture care, specifically by brushing dentures with tooth paste at least twice a day for 2 weeks. Patients were asked to brush palatal mucosa with tooth paste and not to wear their dentures at night. Groups 2 and 3 were directed to keep the dentures in hexetidine after meticulous clean-

Table 2 Pre- and after treatment results for Group 1

		Intragroup comparison of group 1 [fluconazole (n = 21)]			*Two-tailed significance*
		Median	*Min–max*		
Saliva *C. albicans* (cfu ml^{-1})					
Before treatment		2000	500–6000		$z = 4.05$;
After treatment		0	0–600		$P < 0.001$[a]
		After treatment			
	Before treatment	Absent	Present	Total	
Denture *C. albicans*	Absent	7	0	7	$P = 0.002$[b]
	Present	10	4	14	
Lesion *C. albicans*	Total	17	4	21	
	Absent	0	0	0	$P < 0.001$[b]
	Present	15	6	21	
	Total	15	6	21	

[a]Wilcoxon Signed Ranks test.
[b]Mc-Nemar test.

Table 3 Pre- and after treatment results for Group 2

		Intergroup comparison of group 2 [hexetidine] (n = 18)			*Two-tailed significance*
		Median	*Min–max*		
Saliva *C. albicans* (cfu ml^{-1})					
Before treatment		500	0–10 000		$z = 2.94$;
After treatment		0	0–3000		$P = 0.003$[a]
		After treatment			
	Before treatment	Absent	Present	Total	
Denture *C. albicans*	Absent	5	0	5	$P = 0.008$[b]
	Present	8	5	13	
	Total	13	5	18	
Lesion *C. albicans*	Absent	0	0	0	$P < 0.001$[b]
	Present	13	5	18	
	Total	13	5	18	

[a]Wilcoxon Signed Ranks test.
[b]Mc-Nemar test.

Table 4 Pre- and after treatment results for Group 3

		Intragroup comparison of group 3 [fluconazole + hexetidine] (n = 22)			*Two-tailed significance*
		Median	*Min–max*		
Saliva *C. albicans* (cfu ml^{-1})					
Before treatment		2500	0–10 000		$z = 3.94$;
After treatment		0	0–3000		$P < 0.001$[a]
		After treatment			
	Before treatment	Absent	Present	Total	
Denture	Absent	0	0	0	$P = 0.008$[b]
C. albicans	Present	18	4	22	
	Total	18	4	22	
Lesion	Absent	5	0	0	$P < 0.001$[b]
C. albicans	Present	9	8	17	
	Total	14	8	22	

[a]Wilcoxon Signed Ranks test.
[b]Mc-Nemar test.

ing. Any corrective intervention for denture faults was performed if required.

Microbiological investigation
Stimulated saliva and swab samples from the lesion and the fitting surface of dentures were taken from each patient. The sample collections and microbiological examinations were performed at the Department of Microbiology. Saliva was stimulated with a commercially available sugar-free chewing gum and collected into a sterile polypropylene cup during 5 min. The swabs were placed in 1.0 ml Trypticase Soy Broth. The saliva samples were diluted 1:10 in phosphate-buffered saline. One hundred microliters of undiluted and diluted saliva samples and swabs were plated onto a Sabouraud's dextrose agar (Oxoide Ltd, Basingstoke, UK). The plates were incubated at 37°C in air for 48 h and then examined. The yeast colonies of the saliva samples were counted and calculated as the number of colony forming units per milliliters (cfu ml^{-1}). The presence of yeast in the lesion and denture samples were evaluated as present/absent according to their growth on cultures. *Candida albicans* was identified by means of germ tube analysis.

Statistical analysis
All data recorded before and after treatment were evaluated statistically for study groups. Statistical analyses within the groups were performed using the Mc-Nemar and Wilcoxon Signed Rank tests and study between groups were done using the Chi-Square and Kruskall Wallis one-way ANOVA tests. Statistical significance was accepted as $P < 0.05$ and two-tailed.

Results

All patients of the three study groups were compared in terms of age, gender, history of systemic disease, detection of *C. albicans* on denture surfaces and in the lesion and amount of in *C. albicans* saliva samples. There was no statistically significant difference in gender between groups ($P > 0.05$). When the groups were compared in terms of history of systemic disease, group 1 had 13 patients, group 2 had 12 patients and group 3 had 17 patients with systemic disease. No statistically significant difference was found ($P > 0.05$).

The initial quantity of *C. albicans* isolated from saliva samples were between 0 and 10 000 cfu ml^{-1} and there were no statistically significant differences between the three groups ($P > 0.05$). None of the patient groups displayed statistically significant differences in terms of gender, presence of systemic disease and *C. albicans* counts in lesions and dentures ($P > 0.05$) (Table 1).

Table 5 Comparison of all study groups after treatment

	Treatment groups						
	Fluconazole (n = 21)		*Hexetidine (n = 18)*		*Fluconazole + hexetidine (n = 22)*		
	n	*%*	*n*	*%*	*n*	*%*	*Two-tailed significance*
Denture *C. albicans*							
Absent	17	81	13	72	14	64	$\chi^2 = 1.60$[a]; $P = 0.44$
Present	4	19	5	28	8	36	
Total	21	100	18	100	22	100	
Lesion *C. albicans*							
Absent	15	71,4	13	72	18	82	$\chi^2 = 0.76$[a]; $P = 0.68$
Present	6	28.6	5	28	4	18	
Total	21	100	18	100	22	100	
Saliva *C. albicans* (cfu ml^{-1})	Median	Min–max	Median	Min–max	Median	Min–max	
difference from before treatment and after treatment	0	0–3000	0	0–300	0	0–300	$\chi^2_{k.w} = 1.01$; $P = 0.60$

[a]Chi-square test, K.W, Kruskal–Wallis test.

Patients in groups 1, 2 and 3 had a statistically significant decrease in the amount of *C. albicans* in saliva, lesions and dentures after treatment, when compared with pretreatment results ($P < 0.05$) (Tables 2–4). *Candida albicans* counts in saliva, lesions and dentures after treatment detected no statistically significant difference when three groups were compared (Table 5).

Discussion

Candidial colonization and subsequent biofilm formation on denture materials may lead to stomatitis. Daily cleaning of dentures is important in terms of eliminating biofilm formation (Radford *et al*, 1999; Nikawa *et al*, 2003).

A study of Budtz-Jorgersen *et al* (1996) detected denture stomatitis in 72% of denture wearers in an elderly population living in a geriatric institution. The results stated are associated with poor oral hygiene and neglect of denture care. Kulak-Ozkan *et al* (2002) evaluated 70 complete denture wearers clinically and mycologically. They concluded that there exists a statistically significant relationship between denture stomatitis, presence of yeasts and denture cleanliness.

Jeganathan and Lin (1992) reported that comprehensive management of denture stomatitis associated with *C. albicans* included meticulous denture hygiene together with antifungal or antibacterial therapy and correction of denture faults. Our findings are in concordance with these results.

The present study detected no statistically significant differences between the three study groups. This may be a result of applying denture hygiene and keeping dentures in hexetidine during therapy to eliminate candidial colonization. We hypothesize that the formation of biofilm can also be avoided by applying denture hygiene and keeping dentures in hexetidine, and this can therefore prevent the recurrence of oral candidiasis.

Efficacy of fluconazole in oral candidiasis has been investigated by various researchers and successful results have been reported. Although azole derivates are known to be effective, long-term use may cause changes in enzymes of the liver. Additionally, fluconazole has some systemic adverse effects including headaches, skin rash, vomiting, abdominal pain and diarrhea (Bissell *et al*, 1993; Bennet, 1996; Martin Mazuleos *et al*, 1997; Cross *et al*, 1998).

Hexetidine is a very safe oral antiseptic with broad antibacterial and antifungal activity *in vivo* and *in vitro*. It also has very strong antiplaque effects (Kapic *et al*, 2002).

A study of Jones *et al* (1997) concluded that following exposure to hexetidine, the adherence of *C. albicans* to buccal epithelial cells was reduced and proved the role of hexetidine both in superficial candidiasis and systemic complications clinically. However hexetidine mouthrinses may lead to desquamative lesions, discoloration of teeth, restorations and dentures, and gustatory dysfunction as side effects. Such effects are associated with use longer than 3 weeks (Scheie, 1989; Mandel, 1994).

In the present study, as compared with the other two study groups, group 2, where hexetidine was the only medication prescribed, was superior on account of lower likelihood of complications. However, as a side effect, altered taste sensation was reported from two patients in this group. We conclude that dentists should employ a more conservative intervention with oral mouthrinses in order to prevent the adverse effects and complications of systemic drugs for the management of oral candidiasis.

We believe that denture hygiene instructions and use of mouthrinses serve as a more conservative approach. But clinicians must keep in mind that mouthrinses have adverse effects when used for long periods. Duration of treatment with mouthrinses should be no more than 2 weeks and the treatment should be ceased when clinical improvement is visible and the *C. albicans* count is reduced.

References

Bennet EJ (1996). Antimicrobial agents: antifungal agents. In: Hardman JG, Limbird LE, eds. *Goodman& Gilman's The pharmacological basis of therapeutics*, 9th edn. McGraw Hill: New York, pp. 1175–1190.

Bhattacharyya I, Cohen DM, Silverman S (2003). Red and white lesions of the oral mucosa. In: Greenberg MS, Glick M, eds. *Burket's oral medicine, diagnosis and treatment*, 10th edn. BC Decker Inc: Hamilton, Ontario, pp. 85–125.

Bissell V, Felix DH, Wray D (1993). Comparative trial of fluconazole and amphoterisin in the treatment of denture stomatitis. *Oral Surg Oral Med Oral Pathol* **76:** 35–39.

Budtz-Jorgersen E, Mojon P, Banon-Clement JM *et al* (1996). Oral candidosis in long-term hospital care: comparison of edentulous and dentate subjects. *Oral Dis* **2:** 285–290.

Chandra J, Mukherjee PK, Leidich SD *et al* (2001). Antifungal resistance of candidal biofilms formed on denture acrylic in vitro. *J Dent Res* **80:** 903–908.

Chow CK, Matear DW, Lawrence HP (1999). Efficacy of antifungal agents in tissue conditioners in treating candidiasis. *Gerodontology* **16:** 110–118.

Cross LJ, Bagg J, Wray D, Aitchison T (1998). A comparison of fluconazole and itraconazole in the management of denture stomatitis: a pilot study. *J Dent* **26:** 657–664.

Dar-Odeh NS, Shehabi AA (2003). Oral candidosis in patients with removable dentures. *Mycoses* **46:** 187–191.

Ellepola AN, Samaranayake LP (1998). Adhesion of oral *Candida albicans* isolates to denture acrylic following limited exposure to antifungal agents. *Arch Oral Biol* **43:** 999–1007.

Jeganathan S, Lin CC (1992). Denture stomatitis – a review of the aeitology, diagnosis and management. *Aus Dent J* **37:** 107–114.

Jones DS, McGovern JG, Woolfson *et al* (1997). The effects of hexitidine (Oraldene) on the adherence of *Candida albicans* to human buccal epithelial cells *in vitro* and *ex vivo* and on *in vitro* morphogenesis. *Pharm Res* **14:** 1765–1771.

Kapic E, Becic F, Becic E (2002). Hexetidine – an oral antiseptic. *Med Arh* **56:** 43–48.

Kulak-Ozkan Y, Kazazoglu E, Arikan A (2002). Oral hygiene habits, denture cleanliness, presence of yeast and stomatitis in elderly people. *J Oral Rehabil* **29:** 300–304.

Mandel ID (1994). Antimicrobial mouthrinses: overview and update. *J Am Dent Assoc* **125:** 2S–10S.

Martin Mazuleos E, Aller AI, Romero MJ *et al* (1997). Response to fluconazole and itraconazole of *Candida* spp. in denture stomatitis. *Mycoses* **40:** 283–289.

Nikawa H, Jin C, Makihira S *et al* (2003). Biofilm information of *Candida albicans* on the surfaces of deteriorated soft denture lining materials caused by denture cleansers in vitro. *J Oral Rehabil* **30:** 243–250.

Radford DR, Challacombe SJ, Walter JD (1999). Denture plaque and adherence of *Candida albicans* to denture-base materials in vivo and in vitro. *Crit Rev Oral Biol Med* **10:** 99–116.

Scheie A (1989). Modes of action of currently known chemical antiplaque agents other than chlorhexidine. *J Dent Res* **68:** 1909.