



Comparison of the efficacy of indocyanine green-mediated photodynamic therapy and nystatin therapy in treatment of denture stomatitis

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ABSTRACT

Background: *Candida* species have an influence in the pathogenesis of denture stomatitis. The current study aimed to investigate the efficacy of indocyanine green (ICG)-mediated photodynamic therapy (PDT) in combination with nystatin mouthwash (PDT + nystatin) for the treatment of denture stomatitis in comparison with routine antifungal therapy with nystatin alone.

Methods: In this double-blind randomized clinical trial, 66 patients were randomly assigned into PDT + nystatin (n = 33) and nystatin (n = 33) groups, both groups were treated 3-times a day (15 days) with nystatin mouthwash, and PDT was performed twice once a week for the PDT + nystatin group. Briefly, ICG was applied on the palatal lesion and laser irradiation was performed using a diode laser (810 nm, 56 J/cm²). Nystatin group was also treated with sham laser in order to eliminate the possible psychological effects. The clinical and mycological evaluations were carried out at the baseline, during treatment, and the end of follow-up. Patients who completed the treatment and follow-up were eligible for statistical analysis (each group 28 cases).

Results: Patient treatment with nystatin or PDT + nystatin reduced the lesions extension. *Candida* species were isolated from all patients and the number of *Candida* CFU in both groups showed a significant reduction at each post-treatment visit; however, the mean reduction achieved in the PDT + nystatin group was significantly higher than nystatin alone.

Conclusions: ICG-mediated PDT in combination with nystatin mouthwash can improve the clinical feature of denture stomatitis with no adverse effects; therefore, it could be used as an alternative to the currently available antifungal therapy using nystatin alone.

1. Introduction

Denture stomatitis is a fungal infection that affect the supporting palatal mucosa of denture with a prevalence of 15–70% among partial removable or complete denture users [1,2]. Although the etiology of denture stomatitis remains controversial, a variety of systemic conditions and local factors such as hygiene, night wearing, and colonization by opportunistic fungal pathogens, especially *Candida albicans* (*C. albicans*), has been proposed to have a significant role in its pathogenesis [3,4]. Since the majority of cases are infected with *Candida* species, various antifungal agents such as nystatin, clotrimazole, amphotericin B, and chlorhexidine are routinely prescribed as the first-line of treatment for managing denture stomatitis; however, these treatments are

associated with complications such as bitter taste, allergic reactions, adrenal insufficiency, hepatic necrosis, drug interactions, and development of resistance, that potentially limits the usefulness of currently available antifungal agents [2,5–7]. This provides a rationale to develop new therapeutic alternatives.

Combining antifungal agents with other modalities is an alternative strategy that might be more effective [8]. Photodynamic therapy (PDT) is a novel promising modality, suggested as an alternative adjunct to conventional antifungal therapies. Its application relies on the synergic interaction between photosensitizing chemical substances and a visible light with an appropriate wavelength and intensity. In the presence of oxygen molecules, activated photosensitizer induces some reactions, which leads to the death of the targeted cell by generating reactive

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oxygen species [8,9]. Photosensitizer is an important factor in the successful application of PDT, and its different types have been used to treat oral diseases, each having a specific excitation wavelength [10,11]. Indocyanine green (ICG) is a fluorescent dye, used clinically for various diagnostic purposes. It has an optimal peak absorption at 810 nm, which is closer to the absorption peak of most diode lasers and has great potential to be applied as an effective photosensitizer in PDT [12].

To date, several studies were published on the successful application of PDT in oral candidiasis that exhibited antifungal effects against *C. albicans* planktonic cells and biofilms, but most of them are *in-vitro* and *in-vivo* experiments. Although few clinical studies have evaluated the efficacy of PDT in oral candidiasis, their significance was limited due to small sample size and short follow-up period [11,13–19]. Therefore, the current study aimed to investigate the efficacy of ICG-mediated PDT in combination with nystatin mouthwash to treat Iranian patients with denture stomatitis and compare the results with routine antifungal therapy using nystatin alone.

2. Materials and methods

2.1. Ethical approval

The research protocol was approved by the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (IR.SUMS.REC.1397.411), and all participants signed the written informed consent in accordance with the declaration of Helsinki and its later amendment. Additionally, the current study was registered in Iranian Registry of Clinical Trials (registration number: IRCT20120101008585N6).

2.2. Patients

This parallel, double-blind, randomized clinical trial was performed on 66 denture-wearing patients with confirmed clinical evidence of denture stomatitis. Patients were selected from those who had registered at the social club for senior citizens. Each patient's record was evaluated for a subset of demographic and clinical variables, ensuring that none of them had received any medication before their enrolment in the study. Patients with a history of diabetes, immunosuppression, radiotherapy, chemotherapy, or those who had received antibiotics, antifungal agents, or steroids within the past 3 months were excluded. The presence or absence of denture stomatitis was assessed by the same investigator based on the clinical signs and direct observation of the palatal mucosa, classified into three types, as suggested by Newton [20].

2.3. Study design

All patients were blind to their treatments and randomly assigned to one of the PDT + nystatin ($n = 33$) or nystatin ($n = 33$) groups in the form of block randomization. Each block has 4 allocations, consisting 2 allocations for intervention and 2 for the control group. Six possible sequences of treatment allocation in each block were listed and each one was written on a card. Each time, a block was selected and the sequence of treatments registered until the treatment allocations became complete for all patients. The randomization was performed by a methodologist and the allocation concealment was done by the main researcher. On each 66 cards, a sequence was written and sealed. The pockets were put in a box and allocated for each participant based on the order of their enrollment.

Patients in both groups were treated 3 times a day for 15 consecutive days (each 4 min) with a similar volume (20 drops) of commercial nystatin oral drop (100,000 U, manufactured by Jaber Ebne Hayan pharmaceutical, Iran). For the purpose of PDT, the stock solution of ICG (Diagnostic Green GmbH, Germany) at a concentration of 1 mg/

mL was freshly prepared in sterile distilled water and kept in the dark place at room temperature until usage. In the PDT + nystatin group, the ICG was applied on palatal lesion with a sterile swab and after 10 min, the laser irradiation was performed by an experienced operator using the 810 nm diode laser (Polaris2, Poland). The lesions were irradiated in continuous mode for 30 s and fluence of 56 J/cm². Each irradiation point was at a distance of 1 cm from the other, and the same procedure was repeated one week later for each patient (total of two sessions). The participants in the nystatin group received sham laser (off diode laser) in order to eliminate the possible psychological effect. The clinical assessment was performed by another investigator other than PDT operator. Also, mycological assessment was done by a blinded specialist.

2.4. Clinical and mycological assessment

The following parameters were evaluated at the baseline, during treatment (day 15), and the end of follow-up period (day 60): (1) the extension of denture stomatitis according to Newton's classification [20] (0: no palatal inflammation; type I: mild palatal inflammation, type II: affecting most part of palatal mucosa; and type III: granular palatal mucosa); (2) the extension of lesions, which is categorized based on the palatal surface involvement as low (< 25%), medium (25%–75%), and severe (> 75%); (3) *Candida* colony counts, which is quantified as colony forming unit per milliliter (CFU/mL).

To evaluate the *Candida* colony counts before and after each PDT session or sham laser irradiation and also at the end of follow-up period, a sample was obtained by applying a sterile swab on the affected palatal mucosa. Thereafter, the swab was placed in a sterile test tube containing 5 ml of sterile phosphate-buffered saline and vortexed gently to detach the organisms from the swab. Aliquots of the suspension (50 μ l) were directly spread on CHROM agar *Candida* medium (Merck, Germany) and sabouraud dextrose agar (SDA) (Merck, Germany) containing chloramphenicol to identify *Candida* species and quantification of colonies, respectively. The presence of *C. albicans* was confirmed by the typical green colonies grown on CHROM agar *Candida* medium and biochemical tests. Finally, the number of colonies on each SDA plate was counted and the CFU/mL value of each sample was determined.

2.5. Statistical analysis

The statistical analyses were carried out using SPSS software (ver.18, Chicago, USA). To confirm the normal distribution of the data, variables were tested by the Kolmogorov–Smirnov test. The means and standard deviations of CFU count in each treatment groups were compared by paired *t*-test and a *P* value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Patient's characteristics

Overall, 56 patients with denture stomatitis including 13 male (23.2%) and 43 female (76.8%) in the age range of 56–79 years, from those who completed the treatment and the follow-up period, were eligible for the statistical analysis (each group 28 cases). The PDT + nystatin group included 6 (21.4%) male and 22 (78.6%) female with a mean age of 67.6 ± 6.1 years. The nystatin group comprised of 7 (25%) male and 21 (75%) female with a mean age of 67.4 ± 5.3 years. There was no significant difference between PDT + nystatin and nystatin groups in age and gender ($P > 0.05$).

3.2. Evaluation of Newton's classification and extension of the lesions

The results revealed no statistically significant difference between the study groups with respect to Newton's classification and extension of the lesions at the baseline (Table 1). According to Newton's

Table 1
The clinical characteristics of the study population during the course of treatment.

Parameters	Sampling time		Study groups		P value
			PDT + nystatin n = 28	Nystatin n = 28	
Newton's classification	Baseline	Type I	15 (53.6%)	13 (46.4%)	P = 0.693
		Type II	10 (35.7%)	13 (46.4%)	
		Type III	3 (10.7%)	2 (7.1%)	
	Day 15	0	17 (60.7%)	12 (42.9%)	P = 0.353
		Type I	8 (28.6%)	10 (35.7%)	
		Type II	3 (10.7%)	6 (21.4%)	
	Day 60	Type III	0	0	P = 0.007
		0	25 (89.3%)	15 (53.6%)	
		Type I	3 (10.7%)	13 (46.4%)	
Extension of lesions	Baseline	Type II	0	0	P = 0.513
		Type III	0	0	
		Low	1 (3.6%)	2 (7.2%)	
	Day 15	Medium	26 (92.8%)	26 (92.8%)	P = 0.005
		Severe	1 (3.6%)	0	
		Low	27 (96.4%)	18 (64.3%)	
	Day 60	Medium	1 (3.6%)	10 (35.7%)	P = 0.491
		Severe	0	0	
		Low	28 (100%)	26 (92.9%)	
		Medium	0	2 (7.1%)	
		Severe	0	0	

classification, 17 (60.7%) patients in the PDT + nystatin group and 12 (42.9%) patients in the nystatin group had no sign of palatal inflammation at the end of treatment, which increased to 89.3% (25 cases) and 53.6% (15 cases) at the end of follow-up, respectively. There is a statistically significant difference between the groups with respect to the evidence of palatal inflammation achieved at the end of follow-up period (P = 0.007). In addition, our results showed that the extension of lesions was significantly reduced in both groups at each post-treatment visit (Table 1). The disease recurrence was observed in only 2 (7.1%) patients in the nystatin group.

As expected, the *Candida* species isolated from all patients at the beginning of the study without any significant difference in the average of *Candida* colony counts between the groups. The significant reduction was observed in the number of *Candida* CFU at each post-treatment visit as compared to pre-treatment results; however, the mean reduction achieved by the PDT + nystatin group was significantly higher than the nystatin alone (Table 2, and Fig. 1). In each treatment session, the pre- and post-operative number of *Candida* CFU was assessed in the PDT + nystatin group and a significant decrease was observed (P < 0.0001). Moreover, the *Candida* CFU was significantly reduced from the end of session one to the beginning of session two (Table 3, and Fig. 2).

4. Discussion

The etiopathogenesis of denture stomatitis is generally considered to be multifactorial, but *Candida* species are the major pathogens responsible for the development of this chronic disease [21]. Even though

Table 2
Intergroup and intragroup comparison of *Candida* colony counts between the study groups.

Sampling time	Study groups		P value
	PDT + nystatin (n = 28)	nystatin (n = 28)	
Baseline	78.4 ± 53.6	67.9 ± 40.3	P = 0.413
Day 15	22.9 ± 11.1 ^a	35.3 ± 22.5 ^a	P = 0.013
Day 60	2.2 ± 2.6 ^b	15.9 ± 10.5 ^b	P < 0.0001

Intragroup comparison of each parameter in the study groups (^a significant difference between baseline and day 15, ^b significant difference between day 15 and day 60).

clinical applications of PDT and its potential for treatment of localized infections are growing rapidly [12,22], its usage in oral candidiasis are limited due to multi session nature leading to reduced patient adherence [11,13,23,24]. Hence, the present study was designed to evaluate the effect of ICG-mediated PDT combined with conventional nystatin therapy on clinical and microbial outcome of Iranian patients with denture stomatitis.

In this study, *Candida* species were isolated from the palate lesions in all patients. Our findings confirmed the critical role of *Candida* infection in developing denture stomatitis; however, the cause-and-effect relationship has not been fully elucidated. Some denture-related factors and the affinity of *Candida* to the acrylic surface of dentures, combined with reduced oxygen and salivary flow rate in the oral cavity, leads to acidic and anaerobic microenvironment that initializes the colonization of *Candida* species [21,25].

The results revealed that treating patients with nystatin or PDT + nystatin was able to reduce the lesions extension. ICG-mediated PDT improved the clinical features of denture stomatitis and exhibited a marked reduction in the *Candida* CFU in both study groups; however, the mean reduction in PDT + nystatin group was statistically greater. Furthermore, the clinical improvement of the palatal inflammation at the end of follow-up period was observed in 89.3% and 53.6% of patients in PDT + nystatin and nystatin groups, respectively. In spite of two sessions of ICG-mediated PDT, the reduction of *Candida* CFU continued up to day 60, which was more significant in the PDT + nystatin group. In each session of PDT, post-operative samples had a significant lower CFU count than pre-operative ones. None of the type III lesions were completely cured and required to be completed by surgery.

Antimicrobial PDT using ICG has shown to be effective against *Candida* species in some *in-vitro* studies [13,24]. To the best of our knowledge, only five clinical studies were published on the efficacy of PDT on treating denture stomatitis and none of them used ICG as a photosensitizer. However, the continuous CFU count reduction and clinical improvement of denture stomatitis were reported in all the trials [23,26–29]. In line with our results, a clinical remission of denture stomatitis and a significant reduction in *Candida* species CFUs were observed following the methylene blue-mediated PDT in the groups of 5 and 7 patients [26,29]. Additionally, a significant decrease in the clinical signs of denture stomatitis was observed in 60% (3 out of 5) and 80% (4 out of 5) of patients after the application of photodithazine- or photogem-mediated PDT, respectively [27,28]. However, in the photogem-mediated PDT, 2 patients exhibited recurrence during the

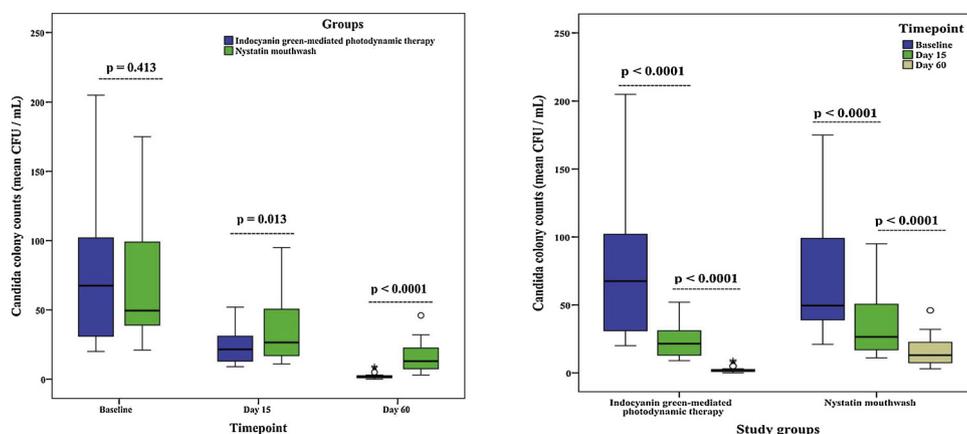


Fig. 1. Assessment of the *Candida* colony counts in the study groups at different timepoint.

Table 3

Comparison of the *Candida* colony counts between the pre- and post-operative samples in PDT + nystatin group.

Treatment sessions	PDT + nystatin group		P value
	Pre-operative	Post-operative	
Session 1 (baseline)	78.4 ± 53.6	39.9 ± 26.4	P < 0.0001
Session 2 (day 15)	22.9 ± 11.1	9.8 ± 5.1	P < 0.0001

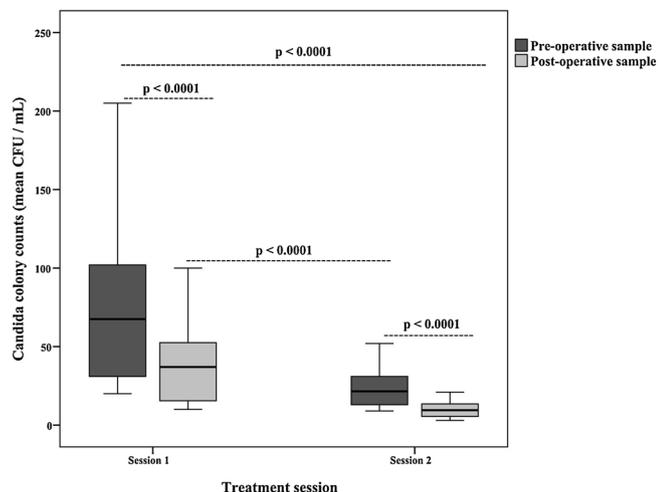


Fig. 2. The effect of indocyanine green-mediated photodynamic therapy on *Candida* colony counts.

follow-up period [28]. The efficacy of photogem-mediated PDT and topical nystatin for treatment of denture stomatitis was also evaluated in a randomized clinical trial study with a clinical success rate of 45% and 53%, respectively [23], which is lower than that of observed in the present study. The accompaniment effects of ICG-mediated PDT and nystatin mouthwash in our study might produce a longer antifungal effect, which justifies the greater success rate. Additionally, the differences in the study design, methodology, and lack of standardization regarding the use of PDT, such as differences in photosensitizers, activation wavelength, power output, irradiation time, and energy dose might be associated with the differences between our results and the aforementioned studies.

PDT mechanism is based on the generation of cytotoxic reactive oxygen species by exposing the diseased tissue to a photosensitizer and light at an appropriate wavelength [8,30]. Since oxygen plays a pivotal role in the success of PDT, ICG has the ability to acts without oxygen molecules, leading to activation and release of free radicals in an

anaerobic area as compared to other photosensitizers (e.g., toluidine blue and methylene blue). Moreover, ICG has the optimal peak absorption at 810 nm which is closer to the absorption peak of most diode lasers. Previous studies showed that depth of ICG penetration was higher than many other photosensitizers. Hence, it is the most suitable IR-photosensitizable molecule which is not toxic and also approved by the US Food and Drug Administration (FDA) for diagnostic purposes in humans. Therefore, ICG can be safely administered for the clinical applications of PDT [12,31–36]. There are some serious drawbacks for photosensitizers such as staining of oral mucosa and teeth. ICG contains some sodium iodide that might cause allergic reaction. The other adverse effects of ICG were also noted in several *in-vitro* and *in-vivo* studies [37–41]. This randomized clinical trial has some important limitations due to methodological flaws such as no prior sample size estimation. It is a fact that elderly patients do not take their medications at the right time, and poor adherence to medications is the first challenge as prescribed; therefore, we used as many case per group as possible. Although no side effect was reported in the present study, further clinical trials with larger sample size and longer follow-ups are warranted to assess the efficacy and safety of ICG-mediated PDT in the treatment of denture stomatitis.

5. Conclusion

This study showed the effectiveness of ICG-mediated PDT in combination with nystatin for the clinical remission of denture stomatitis and significant reduction of *Candida* CFU count. Overall, the prolonged treatment time for routine antifungal therapy and the need for multiple topical or systemic antifungal applications can be substituted by a single or few sessions of antimicrobial PDT.

Conflict of interest

There is no conflict of interest to disclose.

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