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Original Research

Comparison of Er:YAG and Er,Cr:YSGG Laser in the Treatment of Oral Leukoplakia Lesions Refractory to the Local Retinoid Therapy

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Abstract

Objective: The aim of this study was to compare the efficacy of Er:YAG and Er,Cr:YSGG laser in the treatment of oral leukoplakia refractory to conventional retinoid therapy.
***Materials and methods*:** The study sample consisted of 54 patients (16 men and 38 women) who were histopathologically diagnosed with oral leukoplakia that was refractory to conventional retinoid therapy. Patients were randomly allocated into two groups according to the type of the laser used for treatment of oral leukoplakia: Group 1. Er:YAG laser; Group 2. Er,Cr:YSGG laser. Patients were recalled at 6 months and 1 year after treatment to evaluate possible recurrence and assess the patients' postoperative quality of life.
Results: After initial ablation, the degree of residual lesion was significantly greater in the Er:YAG laser group (74.1%), compared with the Er,Cr:YSGG group (18.5%) ($p = 0.0001$). Six months and 1 year after the second ablation, there was no lesion recurrence in either laser group. Fourteen days after the initial ablation, the visual analog scale (VAS) pain rating and the total oral health impact profile score fell significantly in both groups ($p < 0.0001$). However, in the Er,Cr:YSGG laser group, the average value of the VAS rating was significantly lower than in the Er:YAG laser group ($p = 0.039$).
***Conclusions*:** The Er:YAG and Er,Cr:YSGG lasers showed similar efficacy in the treatment of oral leukoplakia and resulted in full postoperative recovery without recurrence after 1 year of follow-up.

Keywords: laser therapy, Er:YAG laser, Er,Cr:YSGG, leukoplakia, precancerous conditions, recurrence

Introduction

Oral leucoplakia is defined by the World Health Organization (WHO) as a lesion on the oral mucosa—which has a white patch or plaque—that cannot be removed by scraping and cannot be classified, clinically or microscopically, as another disease entity.[1] Diagnosis of leucoplakia must include both clinical and histopathological examination. Histopathological examination of clinically diagnosed leucoplakia serves two purposes: to exclude any other type of lesion, and to establish the degree of epithelial dysplasia, if present.[2]

Leucoplakia is a potentially malignant disorder; therefore, squamous cell carcinoma is more likely to occur within these lesions than in normal mucosa.[3] Since most leucoplakias are asymptomatic, the primary goal of treatment must be prevention of malignant transformation. Oral leucoplakia malignancy rates in the published studies are 0.1–17.5% and are dependent on study population, length of follow-up, and treatments applied.[4]

Pharmacological treatment options for oral leucoplakia include carotenoids, retinoids, topical antioxidants, and bleomycin; these treatments are variably successful, with recurrence rates of 5–67% and malignant transformation rates of 8–23%.[5] Surgical treatment options include scalpel excision, electrocoagulation, cryotherapy, and various lasers (CO_2, Er,Cr:YSGG, Nd:YAG, KTP, Er:YAG).[6–8] Notably, there are many advantages to oral laser surgery:

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great visibility within the operative field; precision; enhanced infection control; absence of thermal damage; elimination of bacteremia; almost bloodless surgical and postsurgical period; and minimal need for anesthesia.[9] The CO_2 laser has been thoroughly evaluated in the treatment of oral leukoplakia; it has a reported cure rate of 57–97%,[10,11] an annual recurrence rate of 8–9%[10], and results in a postoperative patient status (pain and swelling) that is similar to conventional treatment approaches.[12] According to a recent report by Nammour et al.,[13] the highest success rate achieved by use of the CO_2 laser is 97.8%, which resulted from complete excision of a ≥1 mm deep leucoplakia lesion along with 3 mm of surrounding healthy tissues. However, thermal laser treatment produces a thin layer of thermally altered tissue around the ablated lesion that demonstrates delayed epithelial regeneration, along with pseudo-dysplastic epithelial artefacts that might result in diagnostic errors.[14]

The use of erbium lasers in oral surgery is highly efficient because of the high water absorption coefficient, compared with the CO_2 laser. Erbium lasers can cut both soft and hard tissues with minimal thermal damage of surrounding epithelial tissue; further, they have shown low induction of inflammatory reactions and more rapid healing.[15,16] Previously, there have been few clinical studies regarding the use of erbium lasers to remove oral leucoplakia;[15,17] the existing studies demonstrate a similar recurrence rate as the CO_2 laser, but report more rapid wound healing.[15,18]

The aim of this clinical study was to evaluate and compare the efficacy of Er:YAG and Er,Cr:YSGG lasers in the treatment of oral leucoplakia, based on subjective and objective postoperative parameters, during a follow-up period of 1 year.

Materials and Methods

Selection of the patients

The study population consisted of 54 patients (38 female and 16 male) (mean age 57.1, median age 62) with homogeneous oral leucoplakia, which had been histopathologically confirmed from biopsy tissue at the Department of Oral Surgery and Oral Medicine, School of Dentistry University of Zagreb, Croatia. The study was performed in accordance with the Helsinki Declaration. The University Ethical Committee approved the study protocol (016/2015) and all patients gave their written informed consent to participate in the study. The study was performed from February 2016 through July 2017.

The patients included in this study demonstrated oral leucoplakia that was refractory to the conventional local therapy that utilized 1% topical isotretinoin in orabase (Roaccutane®, Hoffman-La Roche and Orabase®, ConvaTec, mixed in the same amounts), which was applied on the lesions three times per day for a period of 6 months. Oral lesions in all patients remained persistent and exhibited the same size after 6 months of the conventional treatment. Detailed medical history was recorded for each patient and clinical examination was performed. Only patients who met the criteria for homogenous leucoplakia were included in this study. This study excluded immunocompromised patients on immunosuppressive therapy and patients with any other oral diseases, including those who had been diagnosed or treated for oral cancer.

Clinical examination and laser treatment

Clinical examination included measurement of the size of leucoplakia lesions with a digital scale (Caliper-Digital; Salvin Dental Specialties, Inc., Charlotte, NC); further, the exact localization of each leucoplakia lesion was recorded by sketch in the patient's chart, and data regarding tobacco and alcohol consumption were collected. Examination and documentation of the lesions was performed by the same, independent dentist who was blinded to patient allocation in either of the laser groups. To maintain the blinded nature of the study, each patient was followed using an examination file and a treatment file. The examination file contained information about the patient's detailed medical history and the preoperative/postoperative clinical examinations; this file was accessible only to the examiner, who was unaware of the patient's study group to which the patient was assigned. The treatment file provided data about the randomization modalities; this file was only accessible to the operator.

Patients were randomly allocated into two groups (27 patients per group) by flipping a coin; this specified the laser that would be used for their treatment, and was performed by an independent dentist who did not take part in the study. Importantly, none of the patients knew their assigned treatment group.

In the first group, patients were treated with the Er:YAG laser (LightWalker AT, Fotona, Slovenia) with a noncontact X-Runner digitally controlled handpiece, according to the manufacturer's recommendations, where the integrated scanning mechanism inside the ergonomic box was held in the operator's hand. Size and location of the treatment area were defined directly on the device by the surgeon, according to the shape and size of the lesion. Laser settings were as follows: Quantum Square Pulse (QSP) mode, pulse energy of 120 mJ, frequency of 20 Hz, fluence 18 J/cm^2, and water spray level set at 10 mL/min. Circular, rectangular or hexagonal shape was selected according to the shape of the oral lesion. The distance between the handpiece and the surface of the tissue was fixed at 15 mm (Table 1, Fig. 1).

In the second group, patients were treated with the Er,Cr:YSGG laser (WaterLase iPlus; Biolase LTD) by contact mode, using a sapphire tip MT4 (diameter 0.4 mm). The laser settings were as follows: power of 2.5 W, frequency 50 Hz, fluence 31.25 J/cm^2, and air:water concentration ratio of 25%:60% (Table 1, Fig. 2).

Table 1. Parameters of the Lasers Used in the Study

Laser parameters	*Er:YAG laser*	*Er,Cr:YSGG laser*
Wavelength (nm)	2940	2790
Power density (W/cm^2)	358.20	1984.13
Fluence (J/cm^2)	18	39.68
Frequency (Hz)	20	50
Pulse energy (mJ)	120	50

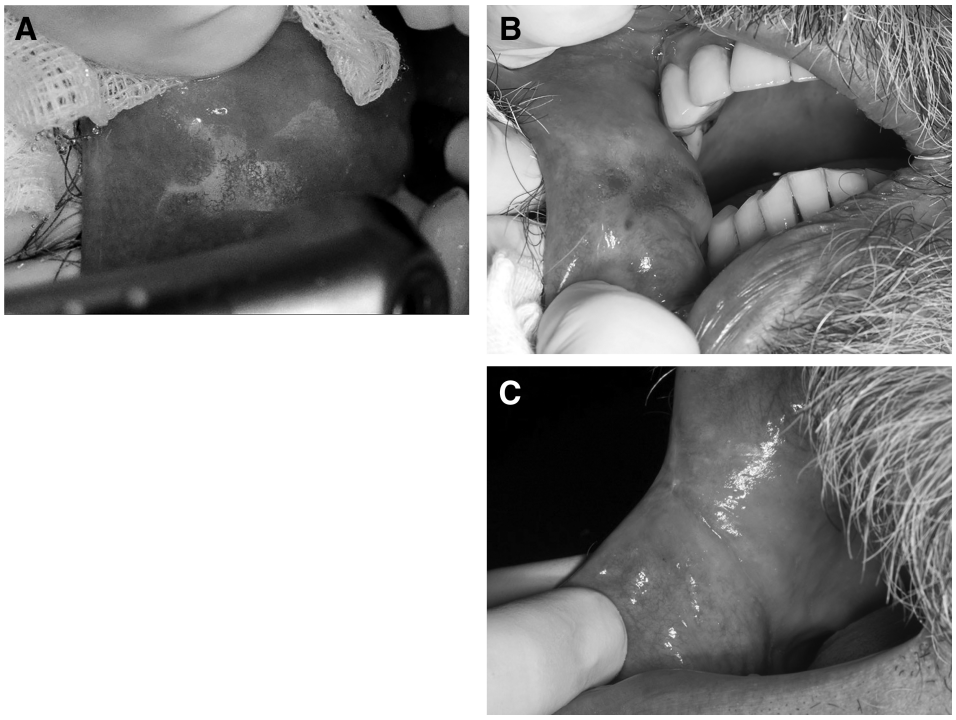

FIG. 1. **(A)** Leucoplakia lesion is ablated with a noncontact X-Runner digitally controlled handpiece of the Er:YAG laser (LightWalker, Fotona). **(B)** Capillary bleeding of the whole ablated lesion. **(C)** Follow-up 3 weeks after surgery.

The local anesthetic articaine (Ubistesin 2%; 3M ESPE, Seefeld, Germany), at a maximum dose of 1.8 mL, was administered before laser treatment in both groups. An infiltrative local anesthesia was used around the lesion, never in the lesion. Anesthesia was always used the same way regardless of the size of the lesion. There were always two applications, one with mesial and the other on the distal side, or one with the vestibular and the other with the oral side, depending on the localization of the lesion. Laser treatment was performed by one surgeon with >5 years of experience using lasers in oral surgery.

After treatment, each patient was provided with detailed postoperative instructions. Patients were recalled and examined on the 7th, 14th, and 28th days after the procedure, and 6 months and 1 year after treatment. At all follow-up visits, if residual lesion was noticed, lesions were remeasured and the laser treatment (final ablation procedure) was performed. Postoperative pain was determined using the visual analog scale (VAS; range 0–10, where 0 is no pain at all and 10 is worst possible pain). Further, each patient filled the Oral Health Impact Profile (OHIP), which consisted of 14 questions regarding the impact of laser treatment on postoperative quality of life.

Evaluation and comparison of laser treatment efficacy was based on number of ablations needed for permanent removal of the leukoplakia, existence of residual lesions, incidences of recurrence and of new lesions, and VAS and OHIP results.

Statistical analysis

The results were analyzed by Fisher's exact test and multivariate variance analysis (MANOVA). All p-values <0.05 were considered significant. For statistical analysis, programme IBM SPSS Statistics version 23.0 (www.spss.com) was used.

Results

From the entire participant cohort, 35.2% ($n=19$) were smokers. The proportion of smokers in both tested groups was similar ($p=1.00$).

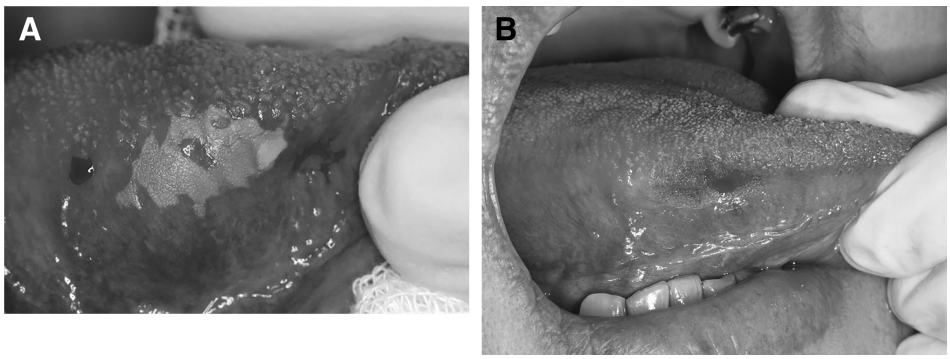

FIG. 2. **(A)** Leucoplakia lesion located on the lateral side of a tongue. **(B)** Capillary bleeding of the ablated lesion on the tongue using the Er,Cr:YSGG laser (WaterLase iPlus, Biolase).

The localization of oral leukoplakia was mainly on the buccal mucosa (33.3%, $n=18$). In male patients, lesions were located most commonly on the buccal mucosa (87.5%, $n=14$), and in female patients on the buccal mucosa and sublingual region (47.4%, $n=18$) ($p<0.0001$). There were no differences in the location of lesions between the two tested groups ($p=0.17$). However, the average size of lesions in the Er;Cr:YSGG laser group was smaller (2.6 cm) than the average size of the lesions in the Er:YAG laser group (7.5 cm) ($p=0.026$).

Twenty-eight days after the first ablation, the rate of the residual lesion was significantly higher in male patients (68.8%, $n=11$) than in female patients (36.8%, $n=0.14$) ($p=0.041$); further, this rate was higher on the buccal surface (48%, $n=12$) than on the surfaces of other sites. Additionally, residual lesions at the same site as the original lesion were significantly more common in the Er:YAG laser group (74.1%), compared with the Er,Cr:YSGG group (18.5%) ($p=0.0001$) (Fig. 3). In these patients, the final ablation procedure was performed using the laser protocol according to their assigned treatment group.

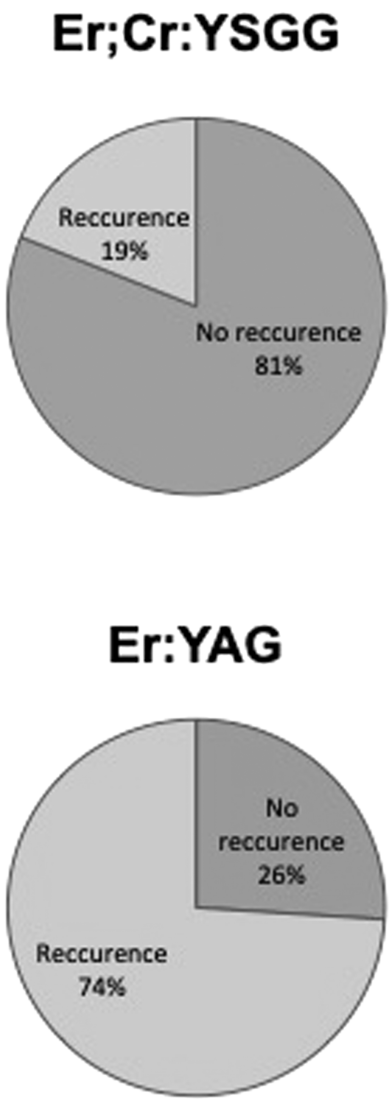

FIG. 3. Recurrence rate of leukoplakia lesions after the first ablation.

At both 6 months and 1 year post-treatment, there were no signs of recurrence or new lesions in either the Er:YAG or the Er,Cr:YSGG laser treated groups.

In both groups, VAS pain ratings and total OHIP scores were significantly lower at 14 days post-treatment, compared with the same scores at 7 days post-treatment ($p<0.0001$) (Figs. 4 and 5). Postoperative pain was reported in 80.8% ($n=42$) of patients at 7 days post-treatment, and by 9.3% ($n=5$) of the patients at 14 days post-treatment. At 7 days post-treatment, there was a significantly higher incidence of postoperative pain in women (92%) than in men (50%) ($p=0.002$). The average VAS rating was significantly lower in the Er,Cr:YSGG laser group (0.0), compared with the Er:YAG laser group (0.4) ($p=0.039$) at 14 days post-treatment (Table 2). Complete healing was observed in all participants within 2 weeks. The postoperative course was normal in all cases; scarring and surgical complications were absent.

Discussion

A variety of lasers (e.g., CO_2, Nd:YAG, KTP, Er:YAG) have been successful in the treatment of oral leukoplakia; further, they exhibit similar recurrence rates that are dependent on the period of follow-up.[15,18–20] In most studies, defocused continuous-wave vaporization with CO_2 laser is the first choice for the treatment of oral leukoplakia.[9,11,13] However, there are some limitations of the CO_2 laser in treatment of nonhomogeneous leukoplakia, which include underdiagnosed incisional biopsies (11.9–29.5%);[21] thermal cytological artefacts, which may be mistaken as dysplasia in oral epithelial biopsies;[14] and high recurrence rates in dysplastic lesions because of difficulty in assessing surgical sites.[22]

The erbium wavelengths exhibit a high affinity for hydroxyapatite, and higher water absorption than other dental laser wavelengths. Therefore, erbium lasers are used in the treatment of dental hard tissues.[23] Additionally, erbium lasers can be used for soft tissue ablation, because soft tissues exhibit high water content.[24] The results of this study showed that both Er:YAG and Er,Cr:YSGG lasers can be used for the ablation of oral leukoplakia without recurrence through 1 year of follow-up. Further, no adverse effects were observed in the postoperative period, thus indicating a significant decrease in pain. Some studies have shown efficacy of the Er:YAG laser in the treatment of oral leukoplakia. Meister et al.[20] reported complete ablation of buccal leukoplakia with the Er:YAG laser (225 J/cm^2); their patient exhibited no recurrence after 1 year of follow-up. Schwartz et al.[15] treated 10 patients, with a total of 16 homogenous leukoplakia lesions (1.5–4 cm in size), with Er:YAG or CO_2 lasers (300 mJ/pulse); they reported complete or partial remission during a follow-up period of 8 months to 1 year.

To our knowledge, only one study has been published on the use of the Er,Cr:YSGG laser in the treatment of oral leukoplakia. Seoane et al.[17] treated four oral leukoplakia lesions with an Er,Cr:YSGG laser (35.7 J/cm^2 per pulse); they concluded that the Er,Cr:YSGG laser induced a minimal amount of thermal artefacts at the surgical

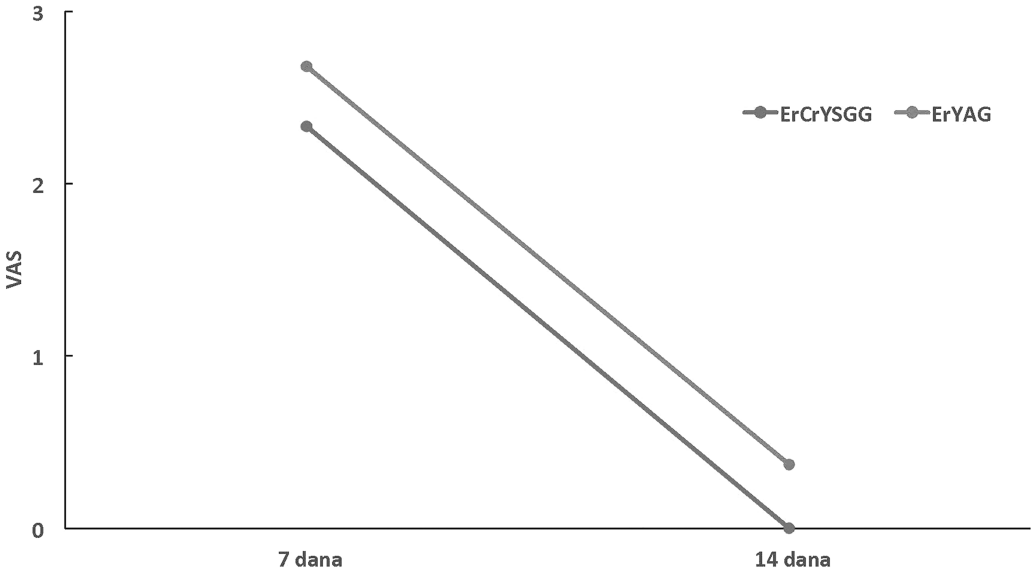

FIG. 4. VAS ratings for patients who received either Er:YAG or Er,Cr:YSGG laser; ratings were collected at 7 and 14 days post-treatment. VAS, visual analog scale.

margins of oral leukoplakias and avoided diagnostic interference with real dysplastic borders. They reported only one recurrence at the same site of the original lesion, 8 weeks post-treatment.[17] However, these results cannot be compared to ours due to the low number of reported cases in their study. In our study, five residual lesions were observed in the Er,Cr:YSGG group at 4 weeks after initial ablation; in contrast, the Er:YAG group exhibited residual lesions in 20 patients at the same follow-up. More residual lesions in the Er:YAG group could result from the significantly greater size of the initial lesion. Also, large differences in VAS scale in initial postoperative measurement can be explained by the size of the lesion in the patients. Since the patients were randomly allocated to two groups, the result was significantly smaller lesions in the Er,Cr:YSGG group compared to the Er.YAG laser (almost three times smaller, 2.6 vs. 7.5 cm). Therefore, the VAS was higher in the Er:YAG group because the ablated surface was larger. The same explanation is for later measurement (VAS scale) during the period of 14 days: larger lesion heals during longer period and often require deeper ablation for complete removal. Also, the higher number of a second treatment in the Er:YAG laser group can be explained by larger initial lesions in the Er:YAG group. Another reason could be noncontact X-Runner digitally controlled handpiece of the Er:YAG laser compared with the contact mode of the Er,Cr:YSGG laser. The digitally controlled mode of laser ablation denotes each individual ablation separately in the exact order specified in the program, meaning that it is not possible to individually ablate particular parts of the lesion that are deeper and each edge of the lesion separately. In a second ablation, the repeated procedure involves wider ablation fields with a greater number of ablation, resulting in ablation to

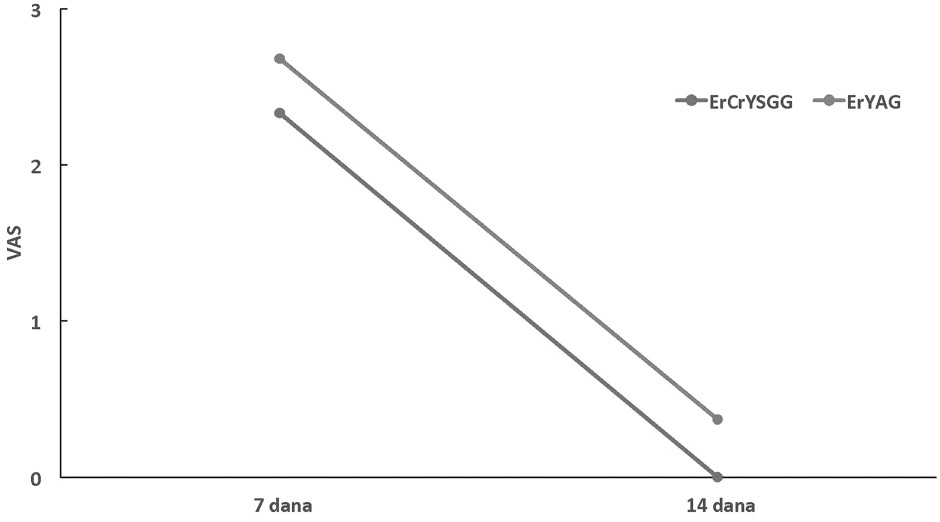

FIG. 5. OHIP scores for patients who received either Er:YAG or Er,Cr:YSGG laser; scores were collected at 7 and 14 days post-treatment. OHIP, oral health impact profile.

Table 2. Comparison of Visual Analog Scale Pain Ratings and Oral Health Impact Profile Scores at 7 and 14 Days Post-Treatment for Both Er:YAG and Er;Cr:YSGG Laser Study Groups

	Total	*Er,Cr:YSGG*	*Er:YAG*	p*
VAS	2.5	2.3	2.7	0.62
OHIP	7.6	5.7	9.6	0.066
VAS 14 days	0.2	0.0	0.4	0.039
VAS 14 days	2.2	1.4	3.1	0.113

OHIP, oral health impact profile; VAS, visual analog scale.

complete capillary bleeding of the whole lesion, which clinically indicates complete removal of the lesion. In the first digital ablation, the procedure was stopped with the first signs of capillary bleeding, which proved to be not good, so a number of digitally ordered ablation was done with more ablation after recurrence, resulting in a deeper layer of removal and a lack of recurrence. Alternatively, the cause of this variation could be attributed to the operator, who may have irradiated (ablated) the lesions too shallowly; moreover, Er:YAG laser wavelengths absorb water at a rate that is three times greater than Er,Cr:YSGG wavelengths, thus resulting in a potential reduction in penetration depth.[25] At 1 year post-treatment, no recurrence was observed in either study group.

Conclusions

The results of this study show that both Er:YAG and Er,Cr:YSGG lasers are efficient in the removal of oral leukoplakia without significant intraoperative or postoperative adverse effects; further, they did not result in recurrence after 1 year of follow-up.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Author Disclosure Statement

All authors declare that they do not have any kind of financial or nonfinancial conflict of interest regarding this study.

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