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Evaluation of Dental Anxiety in Patients Undergoing Second-Stage Surgery with Er, Cr: YSGG Laser Treatment: Randomized Clinical Trial

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ABSTRACT

Oral surgical procedures cause high-pain expectation and consequent anxiety in patients. The aim of this study is to compare the effects of Er, Cr: YSGG laser and scalpel method on dental anxiety level during second-stage implant surgery.

96 patients with 304 osseointegrated implants were divided into two groups. Implants embedded under the oral mucosa were exposed with scalpel or laser surgery. Before the operation the patients were asked to fill the STAI and DAS while resting in the waiting room. In addition, postoperative daily analgesic use, VAS scores perioperativly and on the postoperative 1st, 2nd and 3rd days and demographic information such as age and gender were also recorded.

There was no statistically significant relationship between surgical method and anxiety levels ($p>0.05$. Also, the differences between the scalpel and laser groups in terms of total DAS and STAI scores were statistically insignificant ($p>0.05$). But statistically significant difference was found between surgical method and the analgesic consumption ($p<0.05$). A higher rate of analgesic consumption was observed in the scalpel group.

The use of Er,Cr;YSGG laser could reduce pain during minor oral surgical procedures but had no significant effect on dental anxiety. Different modalities that could provide additional benefits in overcoming this situation should be investigated.

Key Words: Dental Anxiety, Er,Cr:YSGG, Laser Surgery, Minor Oral Surgery, STAI

Introduction

Due to high treatment costs and extended treatment periods of dental implant therapy, the patients' expectations for quality health care and satisfactory treatment outcomes are increasing. (1) Dental lasers, with advantages such as minimal anesthesia requirement, minimal bleeding in surgical field, less surgical trauma and rapid tissue healing, may be preferred as an alternative to conventional methods in uncovering the submerged implants with second stage implant surgery, peri-implant soft tissue management and peri-implantitis treatments. (2) It is known that oral surgical procedures such as implant surgery cause high pain expectation and consequent anxiety in patients. (3) Anxiety is defined as an emotional reaction described as stress, concern, irritability and worry, occurring as a result of an intangible threat or an imminent danger, accompanied by psychosomatic findings such as restlessness, tension, tachycardia and dyspnea. (4,5) There are two types of anxiety, namely "state anxiety" and "trait anxiety". (6) State anxiety refers to the short-term or transient psychological discomfort that develops specifically for a particular situation. Trait anxiety, on the other hand, generally defines a persistent psychological state or personality disorder that develops due to negative experiences in childhood, leading to stress and anxiety in many different situations. (6,7) Dental anxiety or the fear of pain is evaluated in the context of trait anxiety. (8) Dentist fear or anxiety is frequently accompanied poor oral hygiene, decrease in quality of life related to oral health and some psychological disorders such as lack of self-esteem. (9)

Anxiety may result in unsatisfactory treatment outcomes due to deterioration of the physician-patient cooperation during dental procedures, prolongation of treatment time and difficulty in the feasibility of the procedure. (10) Therefore, it

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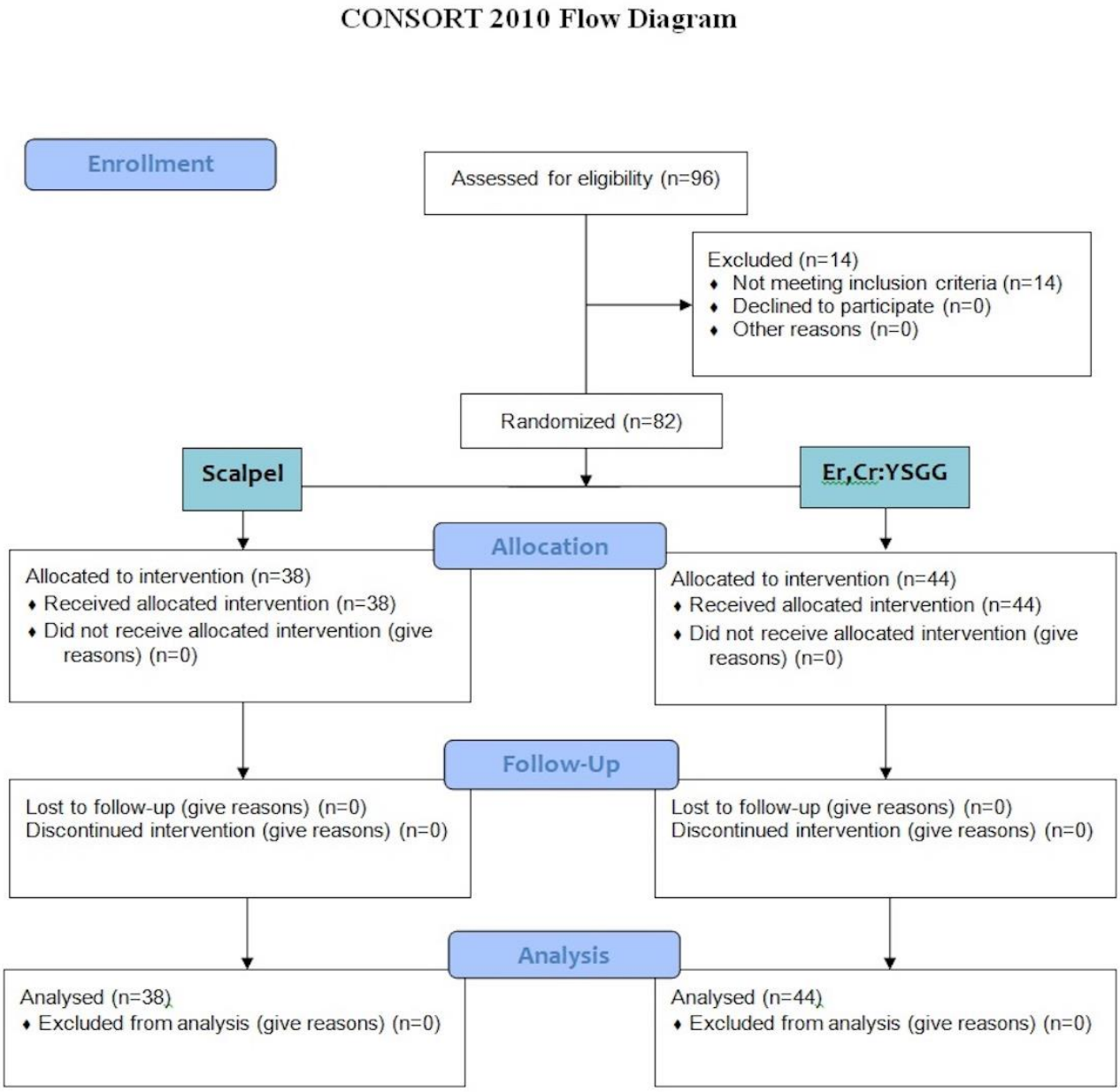

Fig. 1. Flowchart of the patients in the study

is important to assess the dental anxiety and fear level of the patient before the treatment to provide the necessary psychological support to the patient and to reduce the subjective pain and the operation-related stress. (11) For this purpose, the State-Trait Anxiety Inventory (STAI) developed by Spielberger, Gorsuch, Lushene (12) is frequently used. The STAI questionnaire is evaluated together with the Dental Anxiety Scale (DAS) to measure the level of anxiety and fear specific to dental treatments, as it provides information about the general anxiety state of the patient. (13)

The aim of this study is to compare the effects of Er,Cr:YSGG (Erbium, Chromium: Yttrium-Scandium-Gallium-Garnet) laser and traditional scalpel method on dental anxiety level during second stage implant surgery.

Materials and Methods

This study was carried out on 96-healthy individuals, aged between 20-75 years, who underwent dental implant therapy in Van Yuzuncu Yil University, Faculty of Dentistry, Departments of Oral and Maxillofacial Surgery and Periodontology and whose healing caps will be placed after second stage implant surgery. The findings of Eroglu, Ataoglu, Kucuk (14) were used to determine the sample size. According to this, it was calculated that 36 patients each should be included in the experimental and control groups

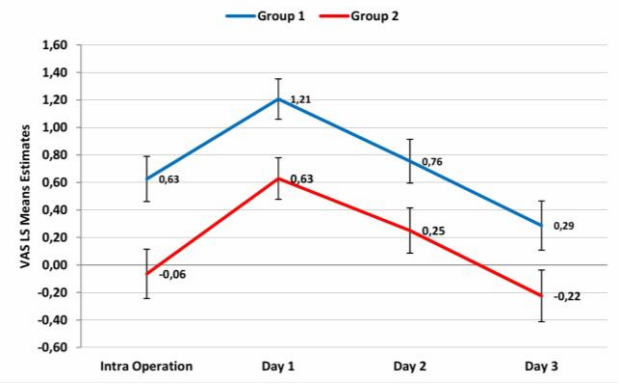

Fig. 2. VAS scores during evaluation times

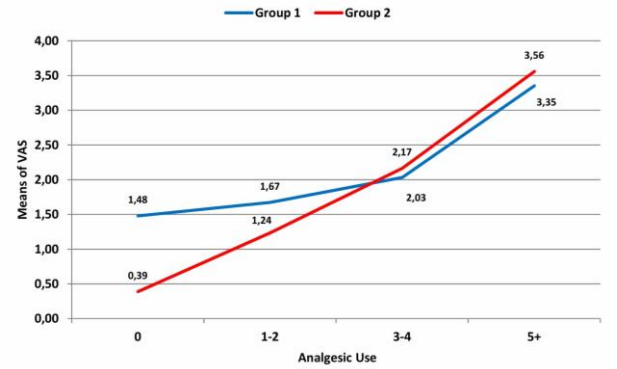

Fig. 3. VAS scores with analgesic use

in order to determine a 50% decrease in dental anxiety levels (β: 0.8, α:0.05). Considering the possible follow-up losses, it was decided that both groups consist of 48 patients. 96 patients were divided into two groups by randomization procedure (GraphPad Prism). The study was approved by Van Yuzuncu Yil University, Faculty of Medicine, Ethics Committee of Clinical Research (Van YYU-01-24.11.2017). Authors declare that there was a preoperative information performed to all of the patients. All surgical procedures were carried out in accordance with the Helsinki Declaration (as revised in Brazil 2013). Before the operation, all patients were informed about the method by which the implants would be exposed and written informed consent was obtained from all participants. The osseointegrated implants embedded under the oral mucosa were exposed with a scalpel (Group 1) or Er,Cr:YSGG laser (Group 2). Totally-304 osseointegrated implants in 96 patients were evaluated clinically and radiographically in detail before the second stage surgical procedures. Patients without sufficient-keratinized gingiva at the implant shoulder region, those the tissue transposition techniques should be applied, those with high DAS score, implants that can not be localized due to gingiva thickness, implants with the possibility of bone overlap on closure screw and scalpel incisions greater than 1 cm length (per implant) were excluded. For these reasons, 10 patients in Group 1 and 4 patients in Group 2 were excluded from the study. After all these evaluations, the second stage implant surgery was initiated with scalpel for 172 osseointegrated implants in 38 patients. The second stage implant surgery of 106 osseointegrated implants (Implant Direct, CA, USA) in 44 patients was performed with Er,Cr:YSGG. Flow chart of the study has been shown in Figure 1.

All surgical procedures were performed by the same surgeon in both groups. In the scalpel group, second stage surgical procedures were carried out with standard technique. Local anesthesia was performed with 2ml of 40mg/ml articaine + 0,012 mg/ml epinephrine (Maxicaine Fort, Vem İlaç San. ve Tic. Ltd. Şti, İstanbul, Türkiye) preoperatively. Incision was made on the area where the closure screw was reflected from the overlying mucosa and the closure screw was exposed. After insertion of the appropriate healing abutment, the procedure was completed by suturing if necessary. In the laser group, Er,Cr:YSGG laser (WaterLase iPlus; USA Biolase Technology Inc., Irvine, CA) with wavelength of 2780 nm was used on "implant recovery" setting suggested by the manufacturer and according to the recommended guidelines (pulse duration of 140-200 μs, repetition frequency of 100 Hz, H mode, output power of 2.75 W, and air/water proportion of 10/10%). MZ5 application tip (550 lm in diameter, 6mm in length, and 1mm in spot size) was used in non-contact mode with target tissue to expose the closure screw and the appropriate healing cap was placed.

The patients were taken to the waiting room on the day of the second stage implant surgery and were asked to fill the STAI and DAS questionnaires for evaluating their anxiety levels. The STAI questionnaire was repeated in the control session (Post-op STAI) one week after the operation in order to verify whether the anxiety levels depend on the patient's general anxiety or due to the surgical procedure. In addition, demographic information such as age and gender, daily analgesic usege after the operation and VAS scores during the operation and on the 1st, 2nd and 3rd days after the operation were recorded. Patients were divided into four groups according to analgesic use. Surgical procedures and patient evaluations (preoperative and postoperative) were

performed by different physicians due to single-blind study design.

Clinical trial registration number ID is NCT03871101 and trial registry name is "Evaluation of Dental Anxiety in Patients Undergoing Second Stage Surgery with Er,Cr:YSGG Laser Treatment: Randomized Clinical Trial".

Evaluation of Anxiety: STAI questionnaire, consisting of two parts with twenty questions each, was used to evaluate the level of state and trait anxiety in the participants (STAI-S: STAI State questionnaire and STAI-T: STAI Trait questionnaire). Both parts were evaluated separately. Patients' answers to each question were scored between 1-4 points. A total of 20-37 anxiety scores were assessed as minimum level of anxiety or none, 38-44 points as moderate and 45-80 as high. (9)

In order to evaluate dental anxiety before treatment, DAS questionnaire consisting of 4 items including multiple choice answers was used. Patients' answers to questions were scored between 1-4 points. The total score of the questions in the questionnaire ranged from 4 to 20, and 4-11 points were interpreted as low level dental anxiety, 12-14 points as moderate and more than 14 points as high.

Statistical Analysis: In the evaluation of the demographic data Chi-squared test was used for the categorical variables to analyse the frequencies and ratios. For continuous variables, Student's *t*-test was used when normal distribution was provided and Mann-Withney U test was used when normal distribution was not provided. In the evaluation of DAS findings, anxiety levels in each group were examined by Chi-squared test. However, Mann-Whitney U test was used to determine the differences between the groups. VAS findings were analyzed by considering the generalized linear mixed model (GLMM) method based on Poisson distribution and AR (1) variance covariance matrix. Correlated p values obtained from the Holm-Tukey multiple comparison method were used for the comparisons of the least squares means in GLMM. In the GLMM model, the effects of the variables (group, time and analgesic consumption) on VAS values and their interactions were modeled. In the analysis of the findings of the STAI-S and STAI-T scales, the cross tabulations of the groups and anxiety categories were examined by the Chi-squared test. Mann-Whitney U test was used for comparisons between groups, and Wilcoxon test was used for intergroup comparisons. p values <0.05 and <0.01 were accepted as statistically significant. All statistical analyzes used in the study were performed on the SAS 9.4 software. In the determination of the power of the statistical tests, the SAS software was used for VAS variables, and the G*Power software was used for the STAI S and T variables.

Results

Descriptive statistics of the data obtained in the study are given in Table 1. The mean age of all individuals was 44.43±12.94, and the mean age of the individuals in Group 1 was higher than Group 2 ($p<0.05$). The study was carried out on 82 patients, 39 females and 43 males. There was no statistically significant difference in gender and age ratios between the groups ($p>0.05$). There was a statistically significant difference between surgical method and the analgesic consumption ($p<0.05$). A higher rate of analgesic use was found in the scalpel group (Table 1). A statistically significant difference was found between the scalpel and laser groups in terms of the number of implants uncovered with second stage implant surgery ($p<0.01$). The number of implants uncovered were less in the laser group compared to the scalpel group.

Table 2 shows the comparison of DAS scores between scalpel and laser groups in terms of anxiety levels. Low level anxiety was found to be 45.21% in the scalpel group and 54.79% in the laser group. Moderate level anxiety was 55.56% in the scalpel group and 44.44% in the laser group. There was no statistically significant relationship between surgical method and anxiety levels ($p>0.05$). High level of DAS score was not observed in any of the groups. There was no statistically significant difference between the scalpel and laser groups in terms of total DAS scores ($p>0.05$).

The results obtained by GLMM method for VAS values, descriptive statistics and least squares means are shown in Table 3. There was a statistically significant difference between scalpel and laser applications ($p<0.05$). Statistically lower VAS values were observed in the laser group compared to the scalpel group. Statistically significant differences were found in both the scalpel and the laser group between intraoperative and postoperative (1st, 2nd, 3rd days) VAS scores. In both groups, VAS was found at the highest level in the first day. The difference between the VAS measurements at 4 time points was compared with the adjusted Tukey-Holm multiple

Table 1. Descriptive statistics for demographic

		Grup 1 (n=38)	Grup 2 (n=44)	Total
		n (%)	n (%)	n (%)
Gender	Female	18 (47.37%)	21 (47.73%)	39 (47.56%)
	Male	20 (52.63%)	23 (52.27%)	43 (52.44%)
		Chi-Square: 0.0011	p value: 0.9741	
Analgesic	0	5 (13.16%)	17 (38.64%)	22 (26.83%)
	1-2	10 (26.32%)	13 (29.55%)	23 (28.05%)
	3-4	14 (36.84%)	7 (15.91%)	21 (25.61%)
	5+	9 (23.68%)	7 (15.91%)	16 (19.51%)
		Chi-Square: 9.13	p value: 0.0276	
		Mean±S.D. Median	Mean±S.D. Median	
		3.44±2.20 4.00	2.11±2.42 1.5	
		Mann-Withney U: 2.89	P value: 0.005	
Implant	1	3 (7.89%)	15 (34.09%)	18 (21.95%)
	2	7 (18.42%)	13 (29.55%)	20 (24.39%)
	3	5 (13.16%)	7 (15.91%)	12 (14.63%)
	4	8 (21.05%)	4 (9.09%)	12 (14.63%)
	5+	15 (39.47%)	5 (11.36%)	20 (24.39%)
		LR Chi-Square: 17.05	p value: 0.0019	
Total implant		172	106	
Age		Mean±Std Dev.	Mean±Std Dev.	Mean±Std Dev.
		47.84±11.48	41.50±12.71	44.43±12.94
		Student t: 2.36	p value: 0.0209	

Table 2. Comparison of Groups for DAS scores

Groups	Anxiety	n (%)	Mean±S.D.	Median (Min.-Max.)	Total Mean±S.D.
Group 1	Low anxiety	33 (45.21%)	6.97±2.14	7 (4-11)	7.74±2.83
	Moderate anxiety	5 (55.56%)	12.80±0.84	13 (12-14)	
Group 2	Low anxiety	40 (54.79%)	7.40±1.88	7.5 (4-11)	7.95±2.53
	Moderate anxiety	4 (44.44%)	13.50±1.00	14 (12-14)	
	p value: 0.5569a				p value: 0.633b

[a] Chi-square for Groups*Anxiety crosstab, [b] Mann Withney U for compare group's total anxiety

comparison values by means of the least squares mean. In both groups, VAS scores on the first day were significantly higher than that of intra-op and post-op 3rd day ($p<0.05$). VAS values of the groups demonstrated a similar variance depending on time. Therefore, there was no statistically significant difference between groups in terms of pain perception by time ($p>0.05$). Changes in VAS scores in both groups depending on time were shown in Figure 2. The effect of analgesic use on VAS score was found to be statistically significant ($p<0.01$), and the mean changes were given in Figure 3. VAS scores in the laser group (mean=0.39) was found to be significantly lower than the scalpel group (mean=1.48) in terms of no need to analgesic use ($p<0.05$). However, there was no significant difference between the VAS values of the groups in terms of increased

Table 3. Results of general linear mixed effects for VAS

		Least Square Means		Descriptive Statistics					GLMM's Results	
Groups	Time	Estimate	Standard Error	Mean	Std. Dev	Median	Min.	Max.	Effect	p value
1	0	0.63	0.16	2.11	2.04	2	0	7	Groups	0.0130
	1	1.21	0.15	3.76	1.82	3	0	9	Time	<0.0001
	2	0.76	0.16	2.39	1.65	2	0	7	Group×Time	0.8650
	3	0.29	0.18	1.50	1.45	1	0	6	Analgesic	<0.0001
2	0	-0.06	0.18	1.23	1.65	0	0	5	Group×Analgesic	0.0098
	1	0.63	0.15	2.45	2.26	2	0	9		
	2	0.25	0.16	1.68	1.96	1	0	9		
	3	-0.22	0.19	1.05	1.49	0	0	5		

0: intra-op, 1: post-op 1st day, 2: post-op 2nd day, 3: post-op 3th day

Table 4. Comparing Scalpel and Laser Groups for STAI-S

	Pre Op Stai-S			Post Op Stai-S		
Anxiety	Group 1	Group 2	Total	Group 1	Group 2	Total
Minimum or not	18 (42.86%)	24 (57.14%)	42	17 (39.53%)	26 (60.47%)	43
Moderate	8 (47.06%)	9 (52.94%)	17	13 (59.09%)	9 (40.91%)	22
High	12 (52.17%)	11 (47.83%)	23	8 (47.06%)	9 (52.94%)	17
	p value: 0.769 a			p value: 0.3258 a		
	Mean±S.D.	Mean±S.D.	p value	Mean±S.D.	Mean±S.D.	p value
	38.87±10.16	36.73±10.87	0.299 b	37.92±9.36	35.86±10.72	0.306 b
	Differences of Means Pre op and Post op STAI S within groups			Wilcoxon p value		
	PRE OP STAI-S - POST OP STAI-S in Group 1 = 0.95			0.471		
	PRE OP STAI-S - POST OP STAI-S in Group 2 = 0.87			0.244		

a: chi square's p value for group*anxiety, **b**: Mann Withney U p value

analgesic use.

In terms of pre-op and post-op STAI-S (STAI State) values, the proportional distribution and mean and standard deviations of individuals' anxiety levels are given in Table 4 together with their statistical findings. In terms of both pre-op and post-op STAI-S scales, there was no statistically significant relationship between the anxiety levels of the scalpel and laser groups ($p>0.05$). Namely, the proportional distribution of the anxiety levels of individuals in groups could be accepted as equal. In addition, the results of pre-op and post-op STAI-S scores were compared between the groups with Mann-Withney U test, and no statistically significant results were found ($p>0.05$). Similarly, there was no significant difference between intergroup comparisons in terms of pre-op and post-op STAI-S scores according to the Wilcoxon test ($p>0.05$).

In terms of pre-op and post-op STAI-T (STAI Trait anxiety score) values, the proportional distribution and mean and standard deviations of anxiety levels of individuals are given in Table 5 together with their statistical findings. In terms of both pre-op and post-op STAI-T scales, there was no statistically significant relationship between the anxiety levels of the scalpel and laser groups ($p>0.05$). That is, the proportional distribution of the anxiety levels of individuals in groups could be accepted as equals. In addition, the results of pre-op and post-op STAI-T scores were compared between the groups with Mann-Withney U test, and no statistically significant results were found ($p>0.05$). Similarly, there was no significant result in intergroup comparisons in terms of pre-op and

Table 5. Comparing Scalpel and Laser Groups for STAI-T

	Pre Op Stai-T			Post Op Stai-T		
Anxiety	Group 1	Group 2	Total	Group 1	Group 2	Total
Minimum or not	8 (32.00%)	17 (68.00%)	25	8 (33.33%)	16 (66.67%)	24
Moderate	18 (50.00%)	18 (50.00%)	36	11 (39.29%)	17 (60.71%)	28
High	12 (57.14%)	9 (42.86%)	21	19 (63.33%)	11(36.67%)	30
	p value: 0.1972 a			p value: 0.0585 a		
	Mean±S.D.	Mean±S.D.	p value	Mean±S.D.	Mean±S.D.	p value
	41.95±6.9	40.45±8.77	0.219b	42.68±6.82	40.68±8.57	0.154b
	Differences of Means Pre op and Post op STAI T within groups			Wilcoxon p value		
	PRE OP STAI-T - POST OP STAI-T in Group 1 = -0.73			0.212		
	PRE OP STAI-T - POST OP STAI-T in Group 2 = -0.23			0.810		

a: chi square's p value for group*anxiety, **b:** Mann Withney U p value

post-op STAI-T according to the Wilcoxon test (p>0.05). For STAI-S, the effect sizes of the pre-op and post-op comparisons were found to be 0.1566 and 0.1580 for Group 1 and Group 2, respectively, and the power of the test was determined as 80.07% and 80.09%, respectively. For STAI-T, these values were found as 0.2008 to 0.052 and 87.52% to 61.33%, respectively.

Discussion

Thanks to its comfortable treatment approach; Er,Cr:YSGG laser has a high acceptability by the patients who undergo minor oral surgery. One the basis of this concept we hypothesized that low anxiety levels can be obtained in second stage implant surgery performed with Er,Cr:YSGG laser compared to the conventional (scalpel) technique. The results of our study showed that there was no significant relationship between the anxiety levels of individuals and the surgical procedure technique. This result is consistent with the results of the studies of some authors. (14,15)

Fear and anxiety in the field of dentistry may be related to the age, gender, education level and personality of the patient. In general, researchers reported that women had higher preoperative anxiety. (13,14,16-20) In our study, in the accordance with some researchers, no statistically significant relation was found between the dental anxiety and age or gender of individuals. (13,21)

It is expected that the anxiety level of an individual who had undergone dental surgery before would decrease in the subsequent procedures.[9] Positive dental procedure experiences will decrease anxiety, while negative experiences will increase anxiety. Informing the patients about the treatment process can trigger additional stress development in individuals. (14) There are many studies in the literature that have different conclusions about the effects of previous experiences on anxiety and fear level. (16,22-25) However, in the researches assesing patients who had undergone implant surgery, it was reported that this procedure caused higher anxiety than other surgical procedures and no difference was observed between genders. (13,26) It was also concluded in this study that the patients who had undergone an implant operation before had a dental anxiety related to the previous operation experience when a second surgical procedure was to be applied and that this anxiety did not show difference between genders.

Weisensee, et al. (17) evaluated the factors affecting pain and anxiety during implant surgery, and concluded that anxiety was adversely affected by pain. It was also reported that this conclusion could offer useful recommendations for clinical practice. However, it was indicated that the individual causes of conditional behavior and phobia could not be obtained by global classification and consequently did not provide recommendations for treatment procedures. (17)

Pain is a highly subjective experience that is influenced by emotions and consciousness. The feeling of pain is not always felt with a harmful stimulus by nociceptor and nociceptive pathways; the psychological state can also cause the feeling of pain. (13) Cabbar, Burdurlu, Tomruk (20) reported that previous surgical experiences did not lead to a statistically significant difference in anxiety levels during subsequent surgical procedures. In this study, we believe that patients who had undergone implant surgery before could associate previous experiences with a simpler

surgical procedure such as second stage implant surgery; so, even if different techniques were to be applied for the second surgery, there was no difference in anxiety levels since the previous operation was the same in both groups.

Fardal and McCulloch (26) reported that the study methods solely limited to the assessment of pain sensation might be inadequate to evaluate the pain perception related to implant surgery. Based on this information, in our study DAS and STAI scales were used together with the VAS scale to confirm the dental anxiety.

Most researchers performed pain and anxiety assessments during the operation, on the 1st day and 1 week after the procedure. In these studies, it was determined that the pain reached the maximum level on the first day after the procedure. In our study, maximum pain level was observed on the 1st postoperative day in both groups, and it was consistent with the literature. (18,27,28)

Baykodi, et al. (29) reported higher scores in the post-op STAI-S questionnaire applied 1 week after the implant operation compared to preoperative scores. In the literature, some researchers found that the anxiety levels measured 1 week after the operation were significantly lower than before the operation. (17) In this study, contrary to both results, the values obtained before the procedure were similar to the STAI-S scores recorded 1 week later. We think that this result may be due to the evaluation of more traumatic procedures (implant surgery, etc.) than second stage implant surgery procedure in other studies. In addition, STAI-S scores in our study were found to be lower in the laser group than in the scalpel group which was consistent with the literature. (5,18,29)

Suyash and Bhatia (30) preferred laser excision in a pediatric patient with a soft tissue lesion, because the child's dental anxiety level was high and so that he would feel less pain with diode laser. Diode laser, blocks the sensory nerves due to the thermal necrosis caused by vaporization in the tissue, decreases the conductivity of neurons and reduces pain via protein denaturation. The authors reported that this method could be used safely even in incompatible pediatric patient groups with high anxiety. (30) Based on this result, it was thought that the anxiety level of the laser group might be lower in this study.

Studies have shown that dental lasers provide significant advantages over conventional surgical procedures, such as minimal bleeding, less tissue trauma, reduced scarring and bacteriostatic effects. (5,31,32) Various lasers can be used for pain control. Liu, et al. (31) reported decreased postoperative pain in children treated with Er.YAG laser. Er,Cr:YSGG laser with 2780 nm wavelength was used in this research and in the literature this device is accepted as one of the lasers that can be used safely. (33) Thus according to the results of this study, statistically significant lower VAS scores were observed in the laser group at all times during and after the operation compared to the scalpel group. In the same way, it was observed that laser significantly reduced the analgesic use in the postoperative period (Fig. 2).

Ugurlu, et al. (5) investigated the effects of dental lasers and rotary instruments on anxiety and observed no difference between the laser and conventional groups. In this study, it was investigated whether Er,Cr:YSGG laser would cause less negative stimuli than scalpel. Based on the results of this study, it can be said that the use of dental laser in second stage implant surgery does not cause a significant change in anxiety compared to conventional technique.

The limitations of this study were that only the use of scalpel and Er,Cr:YSGG laser technique in the second stage implant surgery was assesed, the other lasers and various surgical procedures frequently used in soft tissue have not been evaluated.

Considering the results of the study, it can be said that the use of laser has no significant effect on dental anxiety level compared to scalpel surgery, even though the patients are informed preoperatively about the advantages of laser surgery such as less pain during and after the procedure, minimal or no anesthesia requirement, no need to suturing and decreased postoperative drug use. As a result, it was concluded that the use of Er,Cr;YSGG laser could reduce pain during minor oral surgical procedures but had no significant effect on dental anxiety and that methods that could provide additional benefits in overcoming this situation should be investigated.

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Conflict of Interest: Nil.

Conflict of Interest: The authors declare that they have no conflict of interest.

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Ethical approval: The study was approved by Yüzüncü Yıl University, Faculty of Medicine, Ethics Committee of Clinical Research (YYU-01-24.11.2017).

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

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