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Original Article / Özgün Araştırma

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Effect of Various Laser Systems in Smokers and Non-smokers with Peri-implantitis: A Randomized, Prospective, Single-blind Clinical Trial

Sigara İçen ve İçmeyen Peri-implantitisli Hastalarda Çeşitli Lazer Sistemlerinin Etkisi: Randomize, Prospektif, Tek Kör Klinik Çalışma

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Abstract

Objective: The aim of this study was to evaluate the effects of different laser systems in smokers and nonsmokers with peri-implantitis.

Materials and Methods: Subjects were divided into six groups according to the study protocol: Group 1: Smokers who underwent diode laser application; group 2: Erbium, chromium: Yttrium, scandium, gallium, garnet (Er, Cr: YSGG) laser application. Group 3: smokers undergoing Erbium: Yttrium-aluminum-garnet (Er: YAG) laser application; group 4: non-smokers undergoing diode laser application; group 5: non-smokers undergoing Er,Cr: YSGG laser application; and group 6: non-smokers undergoing Er: YAG laser application. Peri-implant sulcus depth (SD), clinical attachment level (CAL), suppuration, modified plaque index (mPI), gingival index (GI), and modified sulcus bleeding index (mSBI) were recorded, and peri-implant sulcus fluid (PISF) was collected to evaluate osteocalcin.

Results: There were statistically significant differences in the baseline and six-month SD, CAL, mPI, GI, mSBI measurements, and osteocalcin values in all groups ($p<0.05$).

Conclusion: Laser applications for treating peri-implantitis have significantly improved clinical parameters and PISF osteocalcin levels.

Keywords: Bone, dental implants, lasers, osteocalcin, peri-implantitis, risk factors

Öz

Amaç: Bu çalışmanın amacı, peri-implantitis olan sigara içen ve içmeyen hastalarda çeşitli lazer sistemlerinin etkisini değerlendirmektir.

Gereç ve Yöntemler: Çalışma protokolüne göre hastalar altı gruba ayrılmıştır: Grup 1: Sigara içen diyot lazer uygulanan grup; grup 2: sigara içen Erbiyum, kromiyum: yitriyum, skandiyum, galliyum, garnet (Er,Cr: YSGG) lazer uygulanan grup; Grup 3: Sigara içen Erbium: yitriyum-alüminyum-garnet (Er: YAG) lazer uygulanan grup; grup 4: Sigara içmeyen diyot lazer uygulanan grup; grup 5: Sigara içmeyen Er,Cr: YSGG lazer uygulanan grup ve grup 6: sigara içmeyen Er: YAG lazer uygulanan grup. Peri-implant sulkus derinliği (SD), klinik ataşman seviyesi (KAS), süpürasyon, modifiye plak indeksi (mPI), gingival indeks (GI) ve modifiye sulkus kanama indeksi (mSKI) kaydedilmiştir ve peri-implant sulkuler sıvısı osteokalsin seviyesini değerlendirmek için toplanmıştır.

Bulgular: Tüm gruplarda başlangıç ve altı aylık değerlendirmede SD, KAS, mPI, GI, mSKI ölçümleri ve osteokalsin seviyelerinde istatistiksel olarak anlamlı farklılıklar bulunmuştur ($p<0,05$).

Sonuç: Peri-implantitis tedavisinde lazer uygulamaları, klinik parametrelerde ve peri-implant sulkuler sıvı osteokalsin seviyelerinde önemli iyileşmeler sağlamıştır.

Anahtar Kelimeler: Kemik, dental implant, lazerler, osteokalsin, peri-implantitis, risk faktörleri

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Introduction

Today, satisfying results are obtained in an aesthetic and functional sense with dental implant-supported prosthetic approaches (1). However, it is possible to encounter biological complications affecting the tissues around dental implants even in cases of successful osseointegration.

Serum osteocalcin has been shown to be a bone turn-over marker and a clinical diagnostic marker of metabolic bone diseases (2). Kunimatsu et al. (3) showed that no significant amount of osteocalcin was detected in gingivitis whereas osteocalcin levels increased in periodontitis.

Lasers can provide positive outcomes in the treatment of peri-implantitis, since it effectively reaches implant surfaces that cannot be accessed by using mechanical methods and removes the tartar and has bactericidal effects (4). Laser therapy can further contribute to the decontamination of peri-implant tissues, the development of regeneration and healing (5).

In light of all this information, the hypothesis of our study was laser monotherapy provides less improvement in clinical parameters in smokers with peri-implantitis compared to non-smokers with peri-implantitis. This study aimed to evaluate the effect of various laser systems on clinical parameters and peri-implant osteocalcin levels in smokers and non-smokers with peri-implantitis.

Materials and Methods

This study was prepared in accordance with Consort 2010 guidelines (Figure 1). This study was designed as a randomized, prospective, and single-blind clinical trial. Individuals who applied to Kırıkkale University Faculty of Dentistry Department of Periodontology were included in the study. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by Kırıkkale University Clinical Research Ethics Committee (09/02) and the Turkish Medicines and Medical Devices Agency (2019/060). Prior to the study, all individuals to be

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1
	2b	Specific objectives or hypotheses	1
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	2
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	2
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	2
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3
	13b	For each group, losses and exclusions after randomisation, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3
	14b	Why the trial ended or was stopped	3
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	3
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	3
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	3
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	3
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	3
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	3
Other information			
Registration	23	Registration number and name of trial registry	-
Protocol	24	Where the full trial protocol can be accessed, if available	2
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Figure 1. 2010 checklist of information to include when reporting a randomised trial

included in the study were given detailed information about the purpose and the method of the research and informed consent forms were obtained.

Study Groups

A total of 103 implants with peri-implantitis in 42 participants were included in the study: 20 implants of smoking patients undergoing Er:YAG, 15 implants of non-smoking patients undergoing Er:YAG, 19 implants of smoking patients Er,Cr:YSGG laser application, 15 implants of non-smoking patients undergoing Er,Cr:YSGG, 18 implants of smoking patients undergoing diode laser application, and 16 implants of non-smoking patients undergoing diode laser application. Twenty eight participants who did not meet the inclusion criteria were excluded from the study. Simple randomization method was used in the study. Randomization was provided by draw up.

The inclusion criteria were as follows:

1. Presence of a pocket at probing depth of ≥4 mm in at least one implant

2. No mobility of the implant

3. No systemic disease that could affect the outcome of treatment

4. No systemic use of antibiotics in the last six months

5. No peri-implantitis treatment in the last three months

6. Individuals between the ages of 30-60 years.

The exclusion criteria were as follows:

1. Individuals who did not consent to participate in the study

2. Subjects receiving radiotherapy

3. Persons consuming alcohol

4. Presence of pregnancy and lactation

5. Individuals with parafunctional habits such as teeth grinding or bruxism.

Peri-implantitis was diagnosed with the presence of pocket in probing depth of ≥4 mm, radiographic bone loss of >2 mm, bleeding on probing (BoP), and suppuration (present or not) (6). Individuals who smoke at least 10 cigarettes daily for at least 5 years and more are considered to be smokers (7). Groups were created as follows:

Group 1: Smokers treated with a diode laser; **Group 2:** Smokers treated with an Er,Cr:YSGG laser; **Group 3:** Smokers treated with an Er:YAG laser; **Group 4**: Non-smokers treated with a diode laser; **Group 5:** Non-smokers treated with an Er,Cr:YSGG laser; **Group 6:** Non-smokers treated with an Er:YAG laser.

Clinical Measurements

Before the laser applications, clinical periodontal parameters including sulcus depth (SD), clinical attachment level (CAL), suppuration, modified plaque index (mPI), gingival index (GI), mSBI and keratinized mucosa measurements were obtained from all implants and implant sulcus fluid (PISF) was collected. Re-evaluation was performed at the 6th month. The changes in SD and CAL were the primary outcome of this randomized trial and as well as the secondary variables GI, mPI and modified sulcus bleeding index (mSBI). Pressure was applied to the mucosa to determine whether there was an inflammatory flow. It was evaluated dichotomously. All clinical measurements were recorded with a standard, color-coded, discontinuous, pressure calibrated plastic periodontal probe (Click-Probe Blue, Kerr GmbH, Biberach, Germany). All measurements were done by the same examiner (K.B.).

Concentration (ng/mL) = Osteocalcin value x Amount of Dilution (0.2 mL)

PISF volume

Total amount (ng/site) = Osteocalcin concentration x PISF volume (mL)

site (2)

Peri-implantitis Treatment Procedure

After the baseline measurements, patients received treatments (K.B.), the diode laser (Epic10, Settings: 940±10 nm, 2.5W, CP2 mod) was applied for 30 seconds using a 400-µm-thick fiber tip (E4 7 & 9 mm). The laser tip was applied as vertical and horizontal scan along the subgingival implant (8). The procedure was carried out on day 0, 7 and 14.

Pockets were treated using an Er,Cr:YSGG laser (Waterlase, Settings: 1.5 W power, 30 Hz, Water 50%, Air 40%, 50 mJ/pulse, 140 µs pulse duration) by inserting a 14-mm long, 500 µm diameter radial firing tip (RFPT5) into the pocket. The tip was placed at the bottom of the pocket and kept at an angle parallel to the long axis of the implant and epithelial tissue as much as possible. After contact with bone, the tip was slightly retracted and moved up and down in the pocket in the apical-coronal direction with a slow sweeping motion and the buccolingual or mesiodistal direction, depending on the location of the pocket (9).

Er:YAG laser [Fotona, Settings: 100 mJ/pulse (12. 7 J/cm^2), 10 pps, pulse energy of the tip was about 85 mJ/pulse] was applied to the implant surfaces under irrigation using a conical glass fiber tip (R14 CD FIBER TYPE, TAPER 12/0.6). The fiber tip was applied parallel to the implant surface in contact mode or a circular motion from the coronal to the apical direction for 60 seconds with an opening of 10-15 degrees (6).

Statistical Analysis

Power analysis calculations displayed a minimum requirement of 66 samples per group in order to compare data at α=0.05 with a power value of 95%. The statistical significance level in the study was determined as $p<0.05$. Statistical analyses were performed by using IBM SPSS Statistics 22.0 and MS-Excel 2016.

Results

Age and gender distribution of the participants are shown in Table 1. When the sixth-month measurement results were evaluated, it was determined that there was a significant difference among the groups in terms of SD, CAL, mPI, GI and total amount results. Post-hoc test showed that the GI value of patients in the Er,Cr:YSGG laser group was significantly higher than the other groups (Chart 1).

The initial values of the diode laser group revealed that the amount of mPI, concentration and total amount were significantly different in the smoker and non-smoker groups. It was determined that these measurements were higher in the non-smoker group and lower in the smoker group. As a result of the six-month evaluation, the concentration of osteocalcin was found to be seven times higher in the smoker group than the non-smoker group and the difference was also significant in the total amount results (Table 2).

There was a significant difference between the Er,Cr:YSGG laser group and other groups in terms of GI values. The difference in GI was found to be caused by the smoker group which had higher median value. In other clinical measurements, the results in the groups were similar. There was a significant difference between the groups in terms of the six-month total amount. When the clinical evaluation results were examined, there was a significant decrease in sixth-month measurements in all evaluation results (Table 3).

Table 1. Demographic variables

	n (%)		n (%)
Gender		**Smokers**	
Female	54 (52.4)	S+	57 (55.3)
Male	49 (47.6)	S-	46 (44.7)
Laser group		**Age**	
Diode laser	34 (33.0)	Min; max	44; 59
Er,Cr:YSGG laser	34 (33.0)	Mean	54.7
Er:YAG laser	35 (34.0)		

S+: Smoker, S-: Non-smoker, Min: minimum, Max: Maximum

Discussion

It is a very important fact that peri-implant diseases are increasing as implant applications increase. In our study, Er:YAG, Er,Cr:YSGG, diode laser were applied as monotherapy in the treatment of peri-implantitis and clinical measurements such as mPI, GI, SD, CAL, mSBI were observed to decrease significantly. Biochemically, a significant decrease in concentration and the total amount of osteocalcin were observed. The decrease in the total amount was higher in diode laser group than in the other groups.

A meta-analysis examining the relationship between smoking and peri-implantitis shows that smoking can change treatment outcomes in peri-implant diseases (10). In our study, when the smokers and non-smokers in diode laser group were compared according to the initial and six-month results, CAL was found to be significantly higher in the S- group than in the S+ group. The concentration and the total amount of osteocalcin decreased nearly 6 times in the non-smoker group.

Decontamination in peri-implant disease includes mechanical debridement, chemical debridement, laser, antimicrobial photodynamic therapy issues (11). In a study that the efficacy of diode laser as a supportive option to the conventional non-surgical treatment of peri-implant mucositis and initial peri-implantitis are analyzed, twenty-three patients were evaluated and pointed out that diode laser could be used as an adjunct to the conventional non-surgical treatment of peri-implant mucositis and peri-implantitis (12). Mettraux et al. (8) used diode laser in addition to mechanical debridement in their study. In the 2-year follow-up, a significant decrease was observed in SD, BoP, and radiographic bone filling was observed. Al-Falaki et al. (13) evaluated the treatment outcome at 2 and 6 months following the use of Er,Cr:YSGG laser in the non-surgical treatment of peri-implantitis. A significant decrease in BoP was observed in the depth of the sulcus

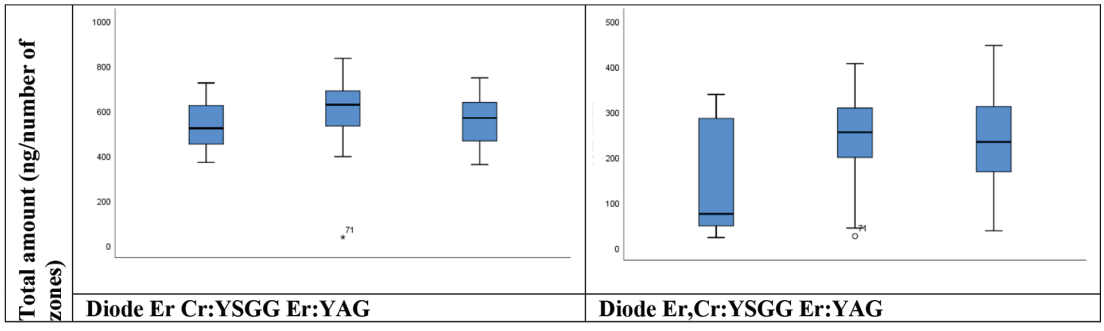

Chart 1. Examination of lasers baseline (T-1) and six-month (T-2) of total amount

T-1: Baseline, T-2: Six-month

Table 2. Examination of lasers baseline (T-1) and six-month (T-2) measurements by smoking status

Variables	Diode laser				Er,Cr:YSGG laser				Er:YAG laser			
	S+[†] groups (n=18)	S-[‡] groups (n=16)	Test	Statistics	S+ groups (n=18)	S- groups (n=16)	Test	Statistics	S+ groups (n=20)	S-groups (n=15)	Test	Statistics
	Median (min; max)	Median (min; max)	Z	p	Median (min; max)	Median (min; max)	Z	p	Median (min; max)	Median (min; max)	Z	p
T-1												
SD	5.0 (4.5; 5.0)	5.0 (5.0; 7.0)	1.944	0.281	5.0 (4.0; 9.0)	5.0 (4.8; 6.0)	1.338	0.202	5.0 (5.0; 6.0)	5.0 (4.5; 6.0)	1.263	0.314
CAL	4.0 (3.5; 4.0)	4.0 (3.5; 6.0)	0.703	0.646	4.0 (2.5; 7.5)	4.0 (3.0; 5.0)	0.232	0.837	4.0 (3.5; 5.0)	4.0 (3.5; 5.0)	0.655	0.542
mPI	3.0 (3.0; 3.0)	2.5 (2.0; 3.0)	4.137	<0.001*	2.0 (2.0; 3.0)	3.0 (2.0; 3.0)	0.533	0.656	2.0 (2.0; 3.0)	3.0 (2.0; 3.0)	1.195	0.283
GI	3.0 (2.0; 3.0)	2.8 (1.5; 3.0)	1.278	0.281	3.0 (2.0; 3.0)	2.0 (2.0; 3.0)	3.351	0.004**	2.0 (2.0; 3.0)	2.0 (2.0; 3.0)	2.421	0.069
mSBI	2.0 (2.0; 2.0)	2.0 (2.0; 2.0)	0.000	1.000	2.0 (2.0; 2.0)	2.0 (1.0; 2.0)	1.616	0.515	2.0 (1.0; 3.0)	2.0 (1.0; 2.0)	1.147	0.542
Concentration	11.2 (6.9; 19.9)	6.3 (5.6; 8.6)	4.623	<0.001*	9.8 (0.5; 18.7)	9.7 (7.2; 15.5)	0.676	0.515	9.6 (4.7; 19.2)	9.1 (6.0; 17.7)	0.633	0.542
Total amount	609.5 (416.0; 723.0)	464.5 (369.0; 567.0)	3.968	<0.001*	622.0 (35.0; 746.0)	683.0 (498.0; 833.0)	1.839	0.066	567.5 (359.0; 746.0)	534.0 (366.0; 722.0)	0.367	0.730
T-2												
SD	3.0 (3.0; 3.0)	3.0 (2.8; 4.3)	0.836	0.551	3.8 (2.3; 6.3)	4.0 (3.0; 4.0)	0.386	0.732	4.0 (3.0; 5.5)	4.0 (3.0; 5.0)	1.068	0.400
CAL	2.0 (2.0; 3.0)	3.0 (2.0; 3.5)	2.912	0.009****	3.0 (2.0; 5.3)	3.0 (2.0; 3.3)	1.737	0.147	3.0 (3.0; 4.5)	3.0 (2.0; 4.0)	0.761	0.564
mPI	1.0 (1.0; 1.0)	1.0 (1.0; 2.0)	2.521	0.126	2.0 (1.0; 2.0)	1.0 (1.0; 2.0)	2.022	0.066	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)	0.302	0.882
GI	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	0.000	1.000	2.0 (1.0; 2.0)	1.5 (1; 2.5)	0.908	0.410	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	0.000	1.000
mSBI	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	0.000	1.000	1.0 (1.0; 1.0)	1.0 (1.0; 2.0)	1.125	0.758	1.0 (1.0; 1.0)	1.0 (1.0; 1.0)	0.000	1.000
Concentration	7.7 (1.8; 16.3)	1.4 (0.6; 3.7)	4.313	<0.001*	6.7 (0.9; 14.9)	5.5 (0.9; 11.9)	0.989	0.336	7.1 (1.5; 10.3)	5.5 (0.9; 10.7)	1.533	0.131
Total amount	271.0 (40; 338)	50.5 (22; 126.0)	3.779	<0.001*	300.0 (25.0; 406.0)	209.0 (43.0; 308.0)	2.637	0.007***	236.0 (75.0; 446.0)	229.0 (37.0; 373.0)	0.833	0.419

[†]S+: Smoker, [‡]S-: Non-smoker

*p<0.001, **p<0.004, ***p<0.007, ****p<0.009. SD: Sulcus depth, CAL: Clinical attachment level, mPI: Modified plaque index, GI: Gingival index, mSBI: Modified sulcus bleeding index

Table 3. Examination of Diode laser, Er,Cr:YSGG laser, Er:YAG laser baseline (T-1) and six-month (T-2) measurements

Variables	Diode laser		Test	Statistics	Er,Cr:YSGG laser		Test	Statistics	Er:YAG laser		Test	Statistics
	T-1 Median (min; max)†	T-2 Median (min; max)‡	Z	p	T-1 Median (min; max)	T-2 Median (min; max)	Z	p	T-1 Median (min; max)	T-2 Median (min; max)	Z	p
SD	5.0 (4.5; 7.0)	3.0 (2.8; 4.3)	5.287	<0.001*	5.0 (4.0; 9.0)	4.0 (2.3; 6.3)	5.119	<0.001*	5.0 (4.5; 6.0)	4.0 (3.0; 5.5)	5.316	<0.001*
CAL	4.0 (3.5; 6.0)	3.0 (2.0; 3.5)	5.164	<0.001*	4.0 (2.5; 7.5)	3.0 (2.0; 5.3)	4.948	<0.001*	4.0 (3.5; 5.0)	3.0 (2.0; 4.5)	5.093	<0.001*
mPI	3.0 (2.0; 3.0)	1.0 (1.0; 2.0)	5.205	<0.001*	2.9 (2.0; 3.0)	1.5 (1.0; 2.0)	4.735	<0.001*	2.5 (2.0; 3.0)	1.0 (1.0; 2.0)	5.273	<0.001*
GI	3.0 (1.5; 3.0)	1.0 (1.0; 1.0)	5.248	<0.001*	3.0 (2.0; 3.0)	1.8 (1.0; 2.5)	5.002	<0.001*	2.0 (2.0; 3.0)	1.0 (1.0; 1.0)	5.445	<0.001*
mSBI	2.0 (2.0; 2.0)	1.0 (1.0; 1.0)	5.831	<0.001*	2.0 (1.0; 2.0)	1.0 (1.0; 2.0)	5.568	<0.001*	2.0 (1.0; 3.0)	1.0 (1.0; 1.0)	5.578	<0.001*
Concentration	8.0 (5.6; 19.9)	2.4 (0.6; 16.3)	4.419	<0.001*	9.8 (0.5; 18.7)	6.0 (0.9; 14.9)	5.001	<0.001*	9.4 (4.7; 19.2)	6.5 (0.9; 10.7)	4.553	<0.001*
Total amount	521.0 (369.0; 723.0)	74.5 (22.0; 338.0)	5.086	<0.001*	626.0 (35.0; 833.0)	254.5 (25.0; 406.0)	5.087	<0.001*	567.0 (359.0; 746.0)	233.0 (37.0; 446.0)	5.078	<0.001*

†max: Maximum; ‡min: Minimum

*p<0.001. SD: Sulcus depth, CAL: Clinical attachment level, mPI: Modified plaque index, GI: Gingival index, mSBI: Modified sulcus bleeding index

and in almost all areas of application. The surface of the implants removed due to peri-implantitis was examined by electronic and microscopic methods. It was observed that almost all of the surfaces of the implants treated with the Er,Cr:YSGG laser are decontaminated (14). Schwarz et al. (15) compared the Er:YAG laser application with mechanical debridement using a plastic curette. The decrease in SD revealed a statistically significant difference in both groups at 12 months. Only BoP values decreased statistically at 24 months, while CAL and BoP decreased significantly at 12 months in both groups. When we evaluate according to clinical parameters in our study, it is seen that three lasers are successful. However, when looking at the change in the total amount, it was observed that there was a 6.99-fold decrease in the diode laser group, 2.45-fold decrease in the Er,Cr:YSGG laser group, and 2.43-fold decrease in the Er:YAG laser group between the initial and the 6th month samples. The limitations of our study are the evaluation of smoking according to the information given by the patient and the lack of serum osteocalcin levels.

Conclusion

This study is a unique clinical study in its field in terms of applying three doses of lasers and comparing various laser wavelengths in the same study, which evaluates the effects of smoking on laser therapy and finds lasers effective in the treatment of peri-implantitis.

Ethics

Ethics Committee Approval: The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by Kırıkkale University Clinical Research Ethics Committee (decision no: 09/02, date: 14.05.2019) and the Turkish Medicines and Medical Devices Agency (2019/060).

Informed Consent: Prior to the study, all individuals to be included in the study were given detailed information about the purpose and the method of the research and informed consent forms were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.B., Concept: K.B., E.O., Design: K.B., E.O., N.D.B., Data Collection or Processing: K.B., E.O., N.D.B., Analysis or Interpretation: K.B., E.O., N.D.B., Literature Search: K.B., E.O., Writing: K.B., E.O., N.D.B.

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Students' Perceptions About the Instructors' Competence in Technology-supported Courses at Dental Faculty: A Cross-sectional Study

Diş Hekimliği Fakültesinde Öğretim Elemanlarının Teknoloji Destekli Sınıflardaki Yeterliklerine İlişkin Öğrenci Algıları: Kesitsel Çalışma

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Abstract

Objective: The pandemic has highlighted the importance of technology-supported courses throughout the world. Evaluating the perceptions of students attending these courses is important to provide high-quality education

Materials and Methods: This study was carried out on 1st, 2nd, and 3rd-grade dentistry students. The "Student Perceptions Scale Regarding the Knowledge of Instructors in Technology - Supported Classrooms" was applied to 207 dentistry students. This scale consists of four sub-dimensions: subject matter knowledge (SMK), technological knowledge (TK), knowledge of students' understanding (KSU), and technological pedagogical content knowledge (TPCK).

Results: SMK, KSU, and TPCK sub-dimension scores did not significantly differ by gender ($p>0.05$). However, the mean TK score of females (3.55±0.47) was found to be significantly higher than that of males (3.28±0.59) ($p=0.001$). There was no statistically significant difference among the SMK, TK, KSU, and TPCK sub-dimension mean scores by age ($p>0.05$). There was a statistically significant difference in the mean scores of the SMK and KSU sub-dimensions by grade (p-values are $p<0.001$ and $p=0.015$ respectively). The mean TK and TPCK sub-dimension scores yielded no significant difference by grade (p-values are $p=0.368$ and $p=0.050$ respectively).

Conclusion: Measuring the quality of technology-assisted teaching and the instructor's TPCK from the student's perspective and determining student perceptions will provide accurate data on the long-term quality of education.

Keywords: Dental education, students, perception, technology-supported course

Öz

Amaç: Pandemi, dünya çapında teknoloji destekli derslerin önemini vurgulamıştır. Bu derslere katılan öğrencilerin oluşan algılarının değerlendirilmesi, bu süreçte kaliteli bir eğitim verilmesi açısından önemlidir.

Gereç ve Yöntemler: Çalışma diş hekimliği 1., 2. ve 3. sınıf öğrencileri ile gerçekleştirmiştir. İki yüz yedi diş hekimliği öğrencisine "Teknoloji Destekli Sınıflarda Öğretim Elemanlarının Bilgilerine İlişkin Öğrenci Algıları Ölçeği" uygulanmıştır. Ölçek, alan bilgisi (AB), teknolojik bilgi (TB), öğrenmeye ilişkin bilgi (ÖİB) ve teknolojik pedagojik alan bilgisi (TPAB) olmak üzere 4 alt boyuttan oluşmaktadır.

Bulgular: TPAB, ÖİB ve AB alt boyutları cinsiyete göre istatistiksel olarak anlamlı farklılık göstermemiştir ($p>0,05$). Ancak kadınların TB puan ortalaması (3,55±0,47) erkeklerinkinden (3,28±0,59) istatistiksel olarak anlamlı farklılık göstermiştir ($p=0,001$). Yaş grupları dikkate alındığında AB, TB, ÖİB ve TPAB puan ortalamaları arasında istatistiksel olarak anlamlı fark bulunmamıştır ($p>0,05$). AB ve

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ÖİB alt boyut puan ortalamaları arasında sınıflara göre istatistiksel olarak anlamlı farklılık görülmüştür (p-değerleri sırasıyla p<0,001 ve p=0,015). TB ve TPAB alt boyut puan ortalamaları sınıflara göre anlamlı bir farklılık göstermemiştir (p-değerleri sırasıyla p=0,368 ve p=0,050).

Sonuç: Teknoloji destekli öğretimin kalitesinin ve öğretim elemanının TPAB'nin öğrenci gözüyle ölçülmesi ve öğrenci algılarının belirlenmesi, eğitimin uzun vadeli kalitesi hakkında doğru veriler sağlayacaktır.

Anahtar Kelimeler: Diş hekimliği eğitimi, öğrenciler, algı, teknoloji destekli ders

Introduction

Technology-assisted teaching and learning resources and methods are widely used to provide qualified learning in higher education (1). The combination of technology, pedagogy, and field knowledge, which are considered to be necessary for the professional development of trainers (2). It is possible to measure the quality of teaching and adequacy of outcomes by making use of the opinions of students (3).

The effects of coronavirus disease-2019 (COVID-19) pandemic revealed the unpreparedness of both instructors and universities in using distance education techniques and educational materials, which are not used widely and extensively in dental education. As in all faculties in Turkey, dental schools' basic and clinical courses were switched to distance education and computer-aided teaching methods.

The present study investigated the students' perceptions about the quality of education provided by instructors through distance education technologies in technology-supported courses and their competence in using technological education tools, as well as students' feedback about the lessons taught during the pandemic.

Materials and Methods

Ethics Statement

Ethical approval was received from the Graduate Education Institute Ethics Committee of Çanakkale Onsekiz Mart University (approval no: 07/36, date: 18.12.2020)

Participants

In the Faculty of Dentistry of Çanakkale Onsekiz Mart University (COMU), all courses, except for the compulsory elective courses, were conducted face to face before the COVID-19 pandemic. After the beginning of the pandemic, all the courses started to be taught online on the Microsoft Teams platform (Microsoft Inc.®) as of the date of 03/23/2020. The present study was carried out with students, who were in the 1st, 2nd, and 3rd years in dental education at Çanakkale Onsekiz Mart University Faculty of Dentistry, during the pandemic period by making use of the Microsoft Teams. The scale was applied to 212 dentistry students of the dental faculty of COMU in Turkey in the academic year of 2020-2021 and the rate of response was 97.6% (n=207). Only the volunteers were involved in this study. The survey was created using Microsoft Forms (Google Inc.®) and the link of the survey was delivered to the students via Microsoft Teams®. Microsoft Forms® was used in collecting the responses. The personal information of the participants was recorded anonymously. Before the data collection, the participants were informed about the study. An e-mail containing a link to the online questionnaire page was sent to the participants, who read the preliminary information and volunteered to participate in the present study. The questionnaire forms were recorded digitally.

Data collection tool: The survey form consists of two parts. The first part consists of a personal information form that includes age, gender, and grade.

The second part of the survey questions the following;

1. "Student perceptions about the instructors degree of knowledge about the aims, information, and ideas of the subject area."

2. "Student perceptions about the instructors' level of knowledge about the digital technologies such as internet, video, interactive whiteboards, and application software."

3. "Student perceptions about the instructors' ability to know students' prior knowledge and to evaluate students' learning in the teaching process and at the end of the subject/unit."

4. "Student perceptions about the instructors' level of technological pedagogical content knowledge (TPCK)."

The "Student Perceptions Scale Regarding the Knowledge of Instructors in Technology - Supported Classrooms" used in the present study was developed by Shih and Chuang (4) and its adaptation to the Turkish language was performed by Şenel et al. (3). The questionnaire consists of a 50-items 5-point Likert-type scale. Scale items were scored as "Never" = 1, "Rarely" = 2, "Sometimes" = 3, "Generally" = 4, and "Always" = 5.

The scale consists of 4 sub-dimensions as subject matter knowledge (SMK) (Items 4-12), Technological Knowledge (TK) (Items 13-23), knowledge of students' understanding (KSU) (Items 24-29), and TPCK (items 30-53).

SMK sub-dimension investigates the students' perceptions about the instructors' aims, knowledge, and ideas in the subject area. TK sub-dimension investigates the students' perceptions about the instructors' knowledge of digital technologies such as the internet, video, interactive whiteboards, and application software. KSU sub-dimension examines the students' perceptions about the instructors' ability to know the students' prior knowledge and to evaluate students' learning in the teaching process and at the end of

the subject/unit. TPCK sub-dimension aims to investigate the students' perceptions about the instructors' TPCK.

Statistical Analysis

The data were analyzed with IBM SPSS V23.0 (SPSS Inc., Chicago, IL, USA). Conformity to normal distribution was examined by Kolmogorov-Smirnov and Shapiro-Wilk tests. The effect of gender, age, and grades on SMK, TK, KSU, TPCK was analyzed with MANOVA. Bonferroni test was used in multiple comparisons. Results are expressed as mean ± standard deviation and median (minimum-maximum) for quantitative data. The significance was set to be $p<0.050$.

Results

The study was conducted on 207 undergraduate dentistry students. 61.4% of the participants were female and 38.6% male respectively. 10.1% of the participants were 18 years old, 82.6% were in the 19-21 age group, and 7.2% were 22 years old. 38.6% of the participants were 1st grade, 34.8% were 2nd grade, and 26.6% were 3rd grade students. The frequency distribution of the demographic characteristics of the participants is presented in Table 1.

When the points given by the participants to the questions to the sub-dimensions in the questionnaire are evaluated, the average SMK score was found to be 3.92, the average TK score to be 3.44, the KSU to be 3.29, and TPCK scores to be 3.42. Descriptive statistics of scale scores are given in Table 2.

Sub-dimensions were evaluated by considering the given points of the participants by different gender, ages, and grades. There was no statistically significant difference among SMK, KSU, TPCK scores by gender ($p>0.05$). The TK scores differ according to gender ($p=0.001$). However, the mean TK score of females (3.55±0.47) was found to be statistically significantly higher than that of males (3.28±0.59) ($p=0.001$). Since only the TK sub-dimension was significant in the evaluation according to gender, the partial eta square value (0.062) was also high only in this dimension (Tables 3, 4).

There was no statistically significant difference among the SMK, TK, KSU, and TPCK sub- dimension mean scores by age ($p>0.05$) (Tables 3, 4).

Considering the grades, there was a statistically significant difference between the mean scores in the SMK sub-dimension ($p<0.001$). The mean point given by the students in the 1st grade was lower than those of the students in the 2nd and 3rd grades ($p<0.05$). There was no statistically significant difference among the 2nd and 3rd grade students regarding the mean points given in SMK ($p>0.05$). While the mean point given by 1st grade students was found to be 3.77±0.38, those of 2nd grade and 3rd grade students were found to be 4.05±0.48 and 3.99±0.37, respectively. The mean TK sub-dimension scores yielded no significant difference by the grades ($p=0.368$) (Tables 3, 4).

Table 1. Frequency distribution of demographic characteristics

	Frequency (n)	Percent (%)
Gender		
Female	127	61.4
Male	80	38.6
Age		
18	21	10.1
19-21	171	82.6
22	15	7.2
Grade		
1st grade	80	38.6
2nd grade	72	34.8
3rd grade	55	26.6

Table 2. Descriptive statistics for scale scores

Sub-dimension	Mean	SD	Median	Minimum	Maximum
SMK	3.92	0.43	4.00	2.56	5.00
TK	3.44	0.54	3.45	1.64	5.00
KSU	3.29	0.74	3.33	1.33	5.00
TPCK	3.42	0.66	3.46	1.50	5.00

SD: Standard deviation, SMK: Subject matter knowledge, TK: Technological knowledge, KSU: Knowledge of students' understanding, TPCK: Technological pedagogical content knowledge

Table 3. Comparison of scale scores

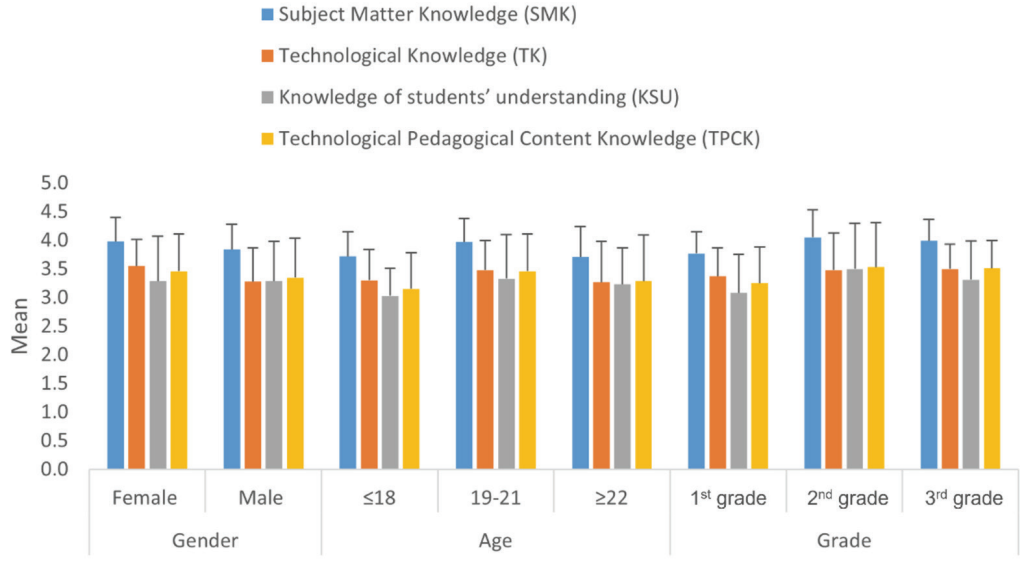
Source	Sub-dimension	F	p-value	Partial eta squared
	SMK	3.027	0.084	0.017
Gender	**TK**	11.864	0.001	0.062
	KSU	0.408	0.524	0.002
	TPCK	1.184	0.278	0.007
Age	**SMK**	2.876	0.059	0.031
	TK	1.311	0.272	0.014
	KSU	0.587	0.557	0.006
	TPCK	1.619	0.201	0.018
Grade	**SMK**	8.693	<0.001	0.088
	TK	1.005	0.368	0.011
	KSU	4.320	0.015	0.046
	TPCK	3.151	0.050	0.034

F: MANOVA test statistic, SMK: Subject matter knowledge, TK: Technological knowledge, KSU: Knowledge of students' understanding, TPCK: Technological pedagogical content knowledge

The mean points given by the students in KSU sub-dimension differed by the grades (p=0.015). The mean point given by the 1st grade students' was found to be lower than that of the 2nd and 3rd grades. And the the mean point given by the 3rd grade students was found to be lower than that of the 2nd grade. While the mean score was found to be 3.08±0.67 in the 1st grade students, the mean score was calculated to be 3.50±0.80 and 3.31±0.68 in the 2nd and 3rd grades, respectively. TPCK sub-dimension mean scores did not differ by grades (p=0.050).

SMK and KSU sub-dimension scores differed by the grades, and examining the partial eta- squared values, it was determined that the effect of grades on SMK was at a higher level. The comparison of scale scores is given in Table 3, whereas the descriptive statistics by gender, age, and grades are given in Table 4, and the descriptive statistics graphs in Graphic 1.

The present study revealed that the gender may affect the perception of technology knowledge sub-dimension in the dental education in favor of males. However, the age groups did not have a similar effect. Moreover, the first-year students have the disadvantages of not knowing their instructors and facing a new educational style.



Graphic 1. Descriptive statistics graphs by gender, age, and grade

Table 4. Descriptive statistics by gender, age, and grade

	Subject matter knowledge	Technological knowledge	Knowledge of students' understanding	Technological pedagogical content knowledge
Gender				
Female	3.98±0.42	3.55±0.47	3.29±0.78	3.46±0.65
Male	3.84±0.44	3.28±0.59	3.29±0.69	3.35±0.68
Age				
≤18	3.72±0.43	3.30±0.54	3.03±0.48	3.15±0.63
19-21	3.97±0.41	3.48±0.52	3.33±0.77	3.46±0.65
≥22	3.71±0.53	3.27±0.71	3.23±0.64	3.29±0.80
Grade				
1st grade	3.77±0.38[a]	3.37±0.50	3.08±0.67[a]	3.25±0.63
2nd grade	4.05±0.48[b]	3.48±0.65	3.50±0.80[b]	3.53±0.78
3rd grade	3.99±0.37[b]	3.50±0.43	3.31±0.68[ab]	3.51±0.49

[a,b]No difference between groups with the same letter

Discussion

In the COVID-19 pandemic, which caused the sudden and mandatory use of tech - supported learning instruments, it was also determined that students and instructors faced several pedagogical, technological, and psychological difficulties (5). Despite these difficulties, it was observed that, after overcoming the problems such as internet connection speed or interruptions, students adapted to the process much faster than instructors. Previous studies revealed that instructors having effective communication skills, teaching style, effective use of technology, flexibility towards teaching, and friendly and supportive attitude successfully managed this process (6).

It was reported in the literature that, in comparison to the face-to-face teaching, teaching in the online media requires different skills in terms of technology and integration (7). It was stated that certain face-to-face approaches may be insufficient for the academicians to use digital instruments and new approaches to teaching and learning should be developed (8).

Measuring the quality of teaching based on the student's feedback and adequacy of the education outcomes has become an important evaluation criterion in education techniques. At this point, tools that measure the quality of technology-supported teaching and the instructors' technological pedagogical field knowledge from the students' perspective will determine these perceptions provide accurate data about the long-term quality of education (3,9).

The scale used in this study was developed by Shih and Chuang (4) and adapted to Turkish by Şenel et al. (5). PCK was defined by Shulman (10) as making a topic understandable to others by using analogies, drawings, examples, explanations, and demonstrations representing it most effectively. PCK enables instructors to know how to help students learn a subject and how to organize and use it in a meaningful way for students having different interests and skills (11). The fact that TPCK mean values did not differ by grades made us think that students had similar expectations in this sub-dimension.

The data obtained in the present study suggest a statistically significant difference in the SMK sub-dimension by the grades. The mean points given by the students in the 1st grade were lower than the other grades. The current students are in the first year of their university education, they only received face-to-face training for five months, unlike other grades, because of the pandemic. Since the first year of dental education is mostly based on acquiring motor manipulation skills and less theoretical education, the translation of this training to online distance education may not have been as successful as in the following grades. Moreover, in the first year of dental education, students may gain insufficient assessment skills because they faced a different education method and the students, who knew their instructors only through online education, had limited opportunity to evaluate them in some courses. However, there was no statistically significant difference between the 2nd and 3rd-grade students in terms of the mean points given in SMK.

In the literature, the word "feedback" is defined as any information that helps students reduce the gap between what they know and what they need to know to complete a task competently (12). Online distance education does not provide face-to-face feedback and peer assessment to the students and it affects the KSU perception of student and causes hesitation in self-evaluation (3,13).

The present study showed that the perception of KSU among the 1st-grade students was lower than the other grades. Students have never met face-to-face with their instructors or classmates during their first year in dental education. In face-to-face education, communicating with the instructor and their peers, they find the opportunity to evaluate themselves unawarely. Both the instructor and the students need direct communication, feedback, and guidance, especially in preclinical courses. The student perception about the instructor's ability to know the students' prior knowledge and evaluate students' learning at the end of the subject/unit is critical (13). The higher KSU perception of 2nd and 3rd grade students supported that the face-to-face interaction with instructors positively influenced the students' KSU perception and, given the data achieved in the present study, this finding corroborates our thoughts specified above.

The perception of TK showed no difference by the grades and corroborated the result that there was no difference between the age groups in terms of TK, KSU, and TPCK scores. Both results did not differ significantly between the groups, and this finding indicates that students' perceptions aged between 18 and 21 years were at the same intensity.

TK scores of males were lower than females and this finding can be interpreted as that the male students expect better technological performance than females do.

Students' perceptions in SMK, TK, KSU, and TPCK did not differ by the age groups. These results suggest that the perceptions of students in the same age group on these issues were similar. Prensky (14) defined the new generation of students as the new native speakers of the digital language used in computers, video games, and the internet and he also named these students "Digital Natives". These students were born into a digital world. As faculty members, we are defined as "digital immigrants" by Prensky (14) since we have involved in this world later in our academic lives. At this point, digital immigrant instructors' outdated language may cause problems in education. Prensky (14) claims that it is challenging to meet students' expectations in technology-supported classrooms because faculty members met technology late but can succeed if they can adapt to change.

Digitalization offers a revolutionary potential for the whole of dental education. It is needed to set generally accepted

standards for digital education among dental faculties and make more use of up-to-date technologies by instructors. It is anticipated that online lectures or demonstrations will become an inseparable part of dental education in the future (15). At this point, it will become a necessity for both instructors and students in dental education to gain sufficient TK in order to use the special materials in education. The impact of the COVID-19 pandemic has caught both instructors and universities unprepared in terms of distance learning techniques and educational materials that have never been used in dental education. Consequently, instructors must be flexible and willing to adapt to the changes. The evolving technological environment and the audience's familiarity will help instructors to integrate into this process.

Conclusion

In the future, the dental education model should be more technology-supported and kept up- to-date. Universities should encourage instructors at this point. Possible problems, which might be encountered in the process of the integration of educators' knowledge, skills, and attitudes into the education in technology-supported classrooms, should be minimized. Moreover, the changes, which affect the adoption and use of technology, should also be determined so that they can use technology effectively in education.

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Ethics

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Authorship Contributions

Concept: Ç.Ç.G., Design: Ç.Ç.G., Y.D., Data Collection or Processing: Ç.Ç.G., C.G., Analysis or Interpretation: Ç.Ç.G., Y.D., C.G., A.D., Literature Search: Ç.Ç.G., Y.D., Writing: Ç.Ç.G., Y.D., C.G., A.D., İ.T.

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Single-visit versus Two-visit Root Canal Treatment of Permanent First Molars in 9-14 Years Old Children

9-14 Yaş Çocuklarda Daimi Birinci Büyük Azı Dişlerinin Tek ve İki Seanslı Kök Kanal Tedavileri

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Abstract

Objective: We aimed to examine the postoperative pain (PP) and 2-year follow-up results of single-visit and two-visit root canal treatment (RCT) applied to the permanent first molars (PFM) of children.

Materials and Methods: Children aged 9-14 years who had a single- or two-visit RCT on their PFM were retrospectively analyzed. Teeth were classified into group 1 (single-visit RCT) and group 2 (two visits RCT). The visual analog scale data, which were routinely recorded the first 48 h after RCT on the anamnesis forms, were used to evaluate PP. The success rate of the RCT in both groups was determined by clinical examination and radiographic evaluation at the end of 2 years, and the Periapical Index (PAI) was used to determine the healing of periapical tissues. Chi-square and Kruskal-Wallis tests were used for statistical analysis.

Results: A total of 51 RCTs, 27 in group 1 and 24 in group 2, were examined. The presence and severity of PP did not significantly differ between the groups (p=0.798). The mean PAI score of group 1 was 1.96±1.13 at the beginning and decreased to 1.81±1 at the end of 2 years. For group 2 it was 2.08±1.59 at the beginning and 2.08±1.35 at the end of 2 years. There was no significant difference between the groups regarding mean preoperative (p=0.683) and postoperative PAI scores (p=0.670).

Conclusions: Single-visit and two-visit RCTs of children showed similar clinical and radiographic results.

Keywords: Single-visit root canal treatment, postoperative pain, flare-up, periapical healing

Öz

Amaç: Çocukların daimi birinci büyük azı (DBBA) dişlerine tek seansta ve iki seansta yapılmış kök kanal tedavilerinin (KKT) postoperatif ağrı ve 2 yıllık takip bulgularının incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Dokuz-14 yaş arası çocuk hastaların kök ucu kapanmış DBBA dişlerine tek veya iki seansta uygulanmış KKT geriye dönük incelenmiştir. Tek seansta KKT yapılmış dişler grup 1, iki seansta KKT yapılmış olan dişler grup 2 olarak ayrılmıştır. Postoperatif ağrının değerlendirilmesinde tedavi sonrası ilk 48 saatte rutin olarak anamnez formlarına kaydedilmiş olan vizüel analog skala verileri kullanılmıştır. Her iki gruptaki KKT'nin 2 yıl sonundaki başarı durumu klinik ve radyografik olarak incelenmiş ve periapikal dokuların iyileşme durumunun belirlenmesinde periapikal indeksinden (PAI) yararlanılmıştır. Verilerin istatistiksel analizinde ki-kare ve Kruskal-Wallis analizleri p<0,05 anlamlılık düzeyinde kullanılmıştır.

Bulgular: İki yılın sonunda 1. grupta 27, 2. grupta 24 olmak üzere toplam 51 KKT incelenmiştir. Gruplar arasında postoperatif ağrının mevcudiyeti ve şiddeti açısından anlamlı farklılık tespit edilmemiştir (p=0,798). Birinci grupun başlangıç PAI skoru ortalaması 1,96±1,13 iken 2 yıl sonunda 1,81±1'e düşmüştür. İkinci grupta ise bu değer başlangıçta 2,08±1,59 ve 2 yıl sonunda 2,08±1,35 olarak tespit edilmiştir. Ortalama PAI skorları açısından başlangıçta (p=0,683) ve 2 yıl sonunda (p=0,670) gruplar arasında anlamlı farklılık olmadığı gözlenmiştir.

Sonuç: Dokuz-14 yaş grubu çocukların DBBA dişlerine tek seansta ve iki seansta yapılmış olan KKT'nin postoperatif ağrı ve 2 yıllık periapikal iyileşme durumu açısından anlamlı farklılık göstermediği tespit edilmiştir.

Anahtar Kelimeler: Tek seansta kök kanal tedavisi, postoperatif ağrı, flare-up, periapikal iyileşme

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Introduction

Root canal treatment (RCT) is based on the principle of maximizing the elimination of intracanal bacteria by mechanical instrumentation, irrigation and calcium hydroxide medicaments placed into the canals. The clinical procedures of RCT which are challenging even by adults, are also difficult to accept by children. Therefore it can often be time-consuming and challenging for both the physician and the child patient. For these reasons, researchers have been working on new techniques, tools and materials in order to make RCT as practical as possible, shorten the chair time and reduce the number of sessions. As a result, single visit RCT have become popular and there are many studies investigating the clinical success of this treatment (1-4).

It was reported that little contraversy exists that teeth diagnosed with irreversible pulpitis should be treated in 1 session (5), but about the cases of pulp necrosis with/without periradicular inflammation the literature is contraversial (6,7). It was reported that mechanical debridement combined with antibacterial irrigation using 0.5% sodium hypochlorite can render only 40-60% of the treated teeth bacteria-negative (8,9). In addition to mechanical debridement and antibacterial irrigation, it has been reported that coating the inside of the canal with calcium hydroxide interappointments can increase the rate of bacteria-negative teeth to around 70% (10). On the other hand, it is stated that RCT completed in single visit not only reduces chair time and cost, but also has a lower flare-up rate (11,12).

It has been observed that studies investigating the clinical success of RCT in single visit were conducted without including patients under the age of 15 (5,13,14). Only one study included patients aged 11-18 years (15). There is insufficient data regarding the rate of flare-up and postoperative pain (PP) or long-term results of single visit RCT of permanent first molars (PFM) in children. Therefore, in this retrospective study, it was aimed to examine the PP and flare-up rates and 2-year follow-up results of single visit RCT applied to the PFM of children, and to compare the findings with two-visit RCT.

Materials and Methods

Ethical approval of the research was received from the Medical Ethics Committee of Pamukkale University (decision number: 15, date: 17.08.2021). In the study, pediatric patients aged 9-14 years who had single or two visit RCT on their PFM by the same physician in Pamukkale University Department of Pediatric Dentistry were analyzed. The anamnesis forms and radiographic records of these patients were investigated retrospectively. The inclusion criteria of PFM with RCT were;

- Presence of a completed root development,
- First time root canal treatment (not the cases of retreatment),
- The cases of irreversible pulpitis or necrotic pulp with or without periapical infection,
- Absence of inflammation drain from the canal (no purulent exudate),
- Absence of widespread periradicular infection beyond the apical 1/3 of the root.

The patients who were consisted of positive patients according to the Frankl behavior scale (16), who had not used antibiotics in the last 1 month before RCT and who could come to the follow-up appointment at the end of 2 years were included in the study. Of the teeth that met the inclusion criteria were named as group 1 those who had single visit RCT and group 2 those who had two visits. Initial periapical status of the treated teeth were evaluated by using the periapical index (PAI) (17) with 5 different scores: 1. Normal periapical structures, 2. Small changes in bone structure, 3. Changes in bone structure with some mineral loss, 4. Periodontitis with well-defined radiolucent area, 5. Severe periodontitis with exacerbating features. When in dubt the higher score is assigned and for multirooted teeth the highest of the scores given to the individual roots is used (17).

In both of the groups, mechanical enstrumentation of the root canals with Reciproc single-file system (size 25 and a taper of 0.06), irrigation with 5% NaOCl, filling with gutta-percha and composite resin restoration of the tooth were performed by the same clinician. In the group 2, additionally root canals dressed with calcium hydroxide and temporary restoration of the tooth were performed in the first visit. Then in the second visit, following the irrigation of calcium hydroxide residues with 5% NaOCl, root filling and restoration procedures completed. Visual analog scale (VAS) (18) scores of the patients which were recorded as none (no pain), slight pain (mild discomfort, need no treatment), moderate pain (pain relieved by analgesics), and severe pain or flare-up (pain and/or swelling not relieved by simple analgesics and required unscheduled visit) on patient anamnesis forms at the end of 6, 12, 24 and 48 hours after treatment were used to evaluate PP. The success rate of the RCT in both groups was determined by the clinical examination and radiographic evaluation and PAI (17) was used again to determine the healing status of periapical tissues after 2 years.

Statistical Analysis

Data were analyzed with the SPSS package program (SPSS v23.0, SPSS Inc., Chicago, IL, USA). Categorical variables were given as numbers and percentages, and the differences between categorical variables were analyzed with chi-square analysis, and data that did not meet the prerequisites of parametric tests were examined with the Kruskal-Wallis test at a significance level of $p<0.05$.

Results

Totally 51 RCT (27 molar teeth in the group 1 and 24 in the group 2) of 32 patients were examined at the end of

2 years. The mean age of the patients participating in the study was 11.47 years. The ratio of male/female was 1 (16 girls/16 boys), and there was no significant difference between the groups (p>0.05). The distribution of the preoperative symptoms of the patients according to the groups is shown in Table 1.

There was PP at a rate of 11.1% and 8.3% in the group 1 and group 2, respectively. Patients who felt PP in both groups stated that the pain started at the end of the first 6 hours and ended within the first 48 hours. 13.0% of the cases who had had preoperative pain in group 1 and 9.0% of the group 2 had PP, too. The presence and severity of PP did not differ significantly between the groups (p=0.798), and VAS 4 or 5 scores were not detected in any of the patients in either group. Findings related to VAS scores are given in Table 2.

While the mean preoperative PAI score of the teeth in group 1 was 1.96±1.13, it decreased to 1.81±1 at the end of 2 years. The mean preoperative PAI score of the teeth in group 2 was 2.08±1.59, and it was calculated as 2.08±1.35 at the end of 2 years. There was no significant difference between the groups about mean preoperative PAI score (p=0.683) and mean postoperative PAI score (p=0.670). The PAI score data of the teeth at the end of 2 years is given in Table 3 and periapical radiographs of a tooth from each group at baseline and after 2 years are shown in Figure 1. The relationship between the presence of preoperative symptoms and PAI findings at the end of 2 years is given in Table 4. Only in group 2, it was observed that the patients with preoperative periapical lesions had significantly higher PAI scores at the end of 2 years (p=0.003).

Table 1. Distrubition of the preoperative symptoms according to groups

Preoperative symptoms	Group 1 %	Group 2 %	p-value*
Spontaneous pain	85.18%	91.66%	0.671
Percussion precision	70.37%	75%	0.712
Periapical radiolucency	62.96%	50%	0.351
Periapical lesion	18.51%	25%	0.574

*p≤0.05 value indicates statistical significance

Table 2. Postoperative VAS scores of the patients

Groups	None n (%)	Slight pain n (%)	Moderate pain n (%)	Severe pain or flare-up n (%)	p-value*
Group 1 n=27	24 (88.9%)	2 (7.4%)	1 (3.7%)	0	0.798
Group 2 n=24	22 (91.7%)	0	2 (8.3%)	0	

VAS: Visual analogue scale. *p≤0.05 value indicates statistical significance

Discussion

According to the results of the study, single-visit and two-visit RCT of PFM of the children did not show significant differences. This result is consistent with most research results in the literature (4,14).

In a study conducted by Risso et al. (15) in adolescents aged 11-18, it was reported that PP was higher in patients who had two-visit RCT than the patients who had single-visit RCT, but the two groups were similar in terms of the severity of the pain. In the study of Paredes-Vieyra and Enriquez (5), including the patients over the age of 16, it was found that a higher rate of PP occurred after two-visit RCT. In another study including patients over the age of 15, it was reported that more PP had occurred in the first 24 hours after two-visit RCT, but the pain status of the patients who had one-visit and two-visit RCT became similar at the end of 48 hours (13).

Although studies examining the success of single-visit and two-visit RCT generally focus on PP and flare-up rate (13,15,19), authorities have stated that PP does not have any effect on the long-term healing success of RCT and therefore, they report that success should be evaluated with long-term clinical and radiographic examinations (20,21). Similarly, in this study, it was observed that PP had no

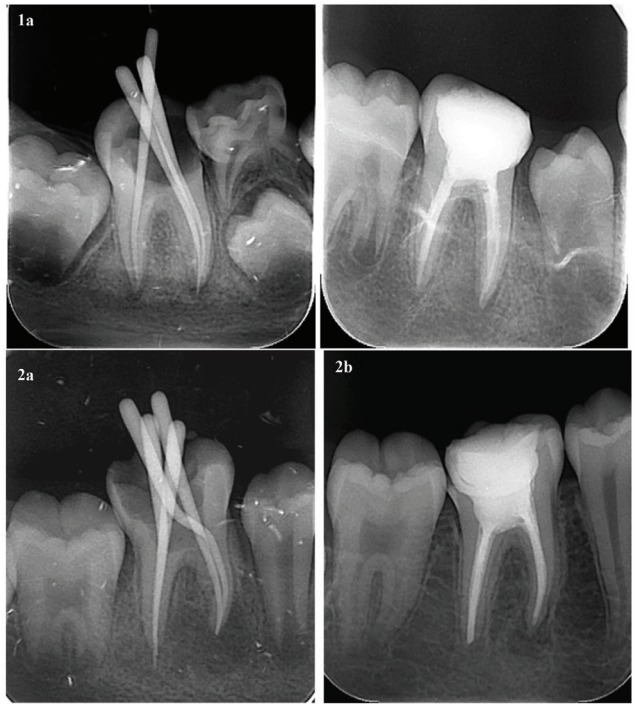

Figure 1. Before and after the root canal treatment (RCT) periapical radiographs of the teeth
1a: Initial periapical radiography of a tooth treated with single-visit RCT. **1b:** Periapical radiography of the same tooth treated with single-visit RCT after 2 years. **2a:** Initial periapical radiography of a tooth treated with two-visit RCT. **2b:** Periapical radiography of the same tooth treated with two-visit RCT after 2 years

effect on the clinical and radiographic findings at the end of 2 years.

It was determined that preoperative symptoms did not have a significant effect on PP or healing status after 2 years. These findings contradict the findings of Risso et al. (15), who stated that there is a significant positive relationship between preoperative pain and PP.

In the study only the patients with preoperative lesions had significantly higher PAI scores at the end of 2 years in group 2. It has been reported that the healing of the periapical lesion can take up to 5 years (22,23) and the healing success of teeth with apical periodontitis is 10-15% lower than those without (21,24). Therefore, in the present study it was not surprising that patients with preoperative periapical lesions had a higher PAI score at the end of 2 years than those without.

The opinion that the success of two- or multiple- visit RCT will be higher than one-visit RCTs because the root canals are disinfected by dressing with calcium hydroxide between the appointments (1,9,10) is not supported by the results of this research. Results of the present study are supporting the report of Manfredi et al. (4) that there is no evidence to suggest that one treatment regimen is better than the other and on the basis of the available evidence that it seems likely that the benefit of a single visit RCT, in terms of time and convenience for both patient and dentist, has the cost of a higher frequency of PP.

In this clinical study including an age group that may have problems of compliance with long-term dental treatments, the attitude of the patients towards RCT completed in one-visit and two-visit was also observed and it seems that one-visit RCT was more challenging for the pediatric patients since the time spent in the chair in one-visit RCT was longer than the time spent in each session of the two-visit RCT. However, one-visit RCT is advantageous in that it can be completed with a single anesthesia application and eliminates the need for re-anesthesia, which is often experienced in the second session of two-visit RCTs. For this reason, one-visit RCT may be a better choice, especially for children who are difficult to persuade to go to the dentist and have fear of injections, however, the time of the treatment should not exceed the tolerance limit of the child, in order to complete the treatment absolutely in one-visit.

Conclusion

As a consequence, no statistical significant difference was observed in terms of periapical healing status at the end of 2 years between the single-visit or two-visit RCTs of the PFM of patients aged 9-14 years. A higher rate of PP was observed after single-visit RCT but this finding is

Table 3. Periapical healing status of the teeth according to the PAI data at the end of 2 years

Groups	Healed (PAI ≤2) n (%)	Not healed (PAI ≥3) n (%)	Improved (decreased PAI) n (%)	Unchanged (same PAI) n (%)	Worse (increased PAI) n (%)
Group 1 n=27	22 (81.48%)	5 (18.52%)	8 (29.62%)	15 (55.55%)	4 (14.81)
Group 2 n=24	16 (66.66%)	8 (33.33%)	6 (25%)	12 (50%)	6 (25)

PAI: Periapical index

Table 4. Relation between the presence of preoperative symptoms and the mean PAI scores at the end of 2 years

Preoperative symptoms		Group 1 PAI at the end of 2 years		Group 2 PAI at the end of 2 years	
		Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)
Percussion	Yes	2.00 ± 1.11	2 (1-4)	2.11 ± 1.49	1 (1-5)
	No	1.38 ± 0.52	1 (1-2)	2 ± 0.89	2 (1-3)
	p-value*	0.238		0.820	
Periapical radiolucency	Yes	1.76 ± 1.03	1 (1-4)	1.83 ± 1.53	1 (1-5)
	No	1.9 ± 0.99	2 (1-4)	2.33 ± 1.15	2,5 (1-4)
	p-value*	0.639		0.219	
Periapical lesion	Yes	2.4 ± 1.14	2 (1-4)	3.33 ± 0.52	3 (3-4)
	No	1.68 ± 0.95	1 (1-4)	1.67 ± 1.28	1 (1-5)
	p-value*	0.165		0.003	

*p≤0.05 value indicates statistical significance. SD: Standard deviation, min: Miminum, max: Maximum, PAI: Periapical index

not statistically significant. Furthermore, the presence of preoperative symptoms did not have a significant effect on PP or signs of periapical healing after 2 years.

Ethics

Ethics Committee Approval: Ethical approval of the research was received from the Medical Ethics Committee of Pamukkale University (decision number: 15, date: 17.08.2021).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: A.İ.G., Concept: C.Ç.E., Design: C.Ç.E., Data Collection or Processing: C.Ç.E., A.İ.G., Analysis or Interpretation: C.Ç.E., Literature Search: C.Ç.E., A.İ.G., Writing: C.Ç.E.

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Original Article / Özgün Araştırma

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Color Stability of Conventional PMMA, Modified MMA and Polyamide Denture Base Materials in Different Beverages

Geleneksel PMMA, Modifiye MMA ve Poliamid Protez Kaide Materyallerinin Farklı İçeceklere Karşı Renk Stabilitesi

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Abstract

Objective: This study aimed to determine how commonly consumed beverages affected the color stability of denture base materials over time.

Materials and Methods: Twenty disks (10.0-mm diameter, 2.0-mm thick) of conventional polymethylmethacrylate (PMMA) (Meliodent), modified methyl methacrylate monomer (MMA) (Bre-Crystal and Acryfee), and polyamide (Bre-Flex, Flexinylon, and T Crystal) acrylic resins with smooth and rough surfaces were prepared. The color of the specimens was measured using a colorimeter at that time (T0). Each specimen was immersed in coffee, coke, tea, and distilled water. The color of the specimens was measured again after 1-day (T1), 12-day (T2), and 36-day (T3) immersion periods. The CIE L*a*b* system was used to calculate the mean color changes for each material, which were then statistically compared using repeated measures ANOVA and Bonferroni intervals at 0.95.

Results: Regardless of time or beverage, there was no significant difference between smooth and rough surfaces ($p>0.05$). Across all time intervals, the modified MMA (Bre-cystal) demonstrated a statistically significantly lower color difference ($p<0.05$). Regardless of time, modified MMA (Acryfree) and conventional PMMA (Meliodent) specimens exposed to coke demonstrated significantly lower color stability than all others ($p<0.05$).

Conclusion: Beverages did not cause a statistically significant color change compared with distilled water after T1 and T3 periods. According to the NBS system, the color changes after the T3 period were between "slight" and "much". Modified MMA resin (Bre-Crystal) can be used as a denture base material in patients with PMMA allergy because of its high color stability in long-term use.

Keywords: Color stability, denture base, acrylic resin, PMMA, modified MMA, polyamide, polymers

Öz

Amaç: Bu çalışmanın amacı, yaygın olarak tüketilen içeceklerin farklı zaman aralıklarında protez kaide materyallerinin renk stabilitesi üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntemler: Konvansiyonel polimetilmetakrilat (PMMA) (Meliodent), modifiye metilmetakrilat (MMA) (Bre-Crystal ve Acryfee) ve poliamid (Bre-Flex, Flexinylon ve T Crystal) akrilik rezinlerden oluşan 20 disk şeklinde (10 mm çap, 2 mm kalınlık) örnek pürüzsüz ve pürüzlü yüzeylerde hazırlandı. Tüm örneklerin başlangıç rengi kolorimetre ile ölçüldü (T0). Her örnek kahve, kola, çay ve distile suya daldırıldı. Örneklerin rengi 1 günlük (T1), 12 günlük (T2) ve 36 günlük (T3) daldırma sürelerinden sonra tekrar ölçüldü. Her örnek için ortalama renk değişikliklerini (ΔE) hesaplamak için CIE L*a*b* sistemi kullanıldı. Elde edilen veriler 0,95 güven aralığında ANOVA ve Bonferroni testleri kullanılarak istatistiksel olarak karşılaştırıldı.

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Bulgular: Pürüzsüz ve pürüzlü yüzeyler arasında renk değişimi açısından zaman veya içecekten bağımsız olarak anlamlı fark yoktu (p>0,05). Tüm zaman aralıklarında, modifiye MMA (Bre-cystal) daha yüksek renk stabilitesi gösterdi (p<0,05). Zamandan bağımsız olarak, kolaya daldırılan modifiye MMA (Acryfree) ve konvansiyonel PMMA (Meliodent) örnekleri, istatistiksel olarak anlamlı derecede daha düşük renk stabilitesi sergiledi (p<0,05).

Sonuç: Çalışmada kullanılan içecekler, T1 ve T3 periyodlarından sonra distile suya göre istatistiksel olarak anlamlı bir renk değişimine neden olmadı. NBS sistemine göre T3 periyodundan sonra renk değişimleri "hafif" ile "çok" arasındaydı. Modifiye MMA rezin (Bre-crystal), uzun süreli kullanımda yüksek renk stabilitesi nedeniyle PMMA alerjisi olan hastalarda protez kaide materyali olarak öne çıkabilir.

Anahtar Kelimeler: Renk stabilitesi, protez kaidesi, akrilik rezin, PMMA, modifiye MMA, poliamid, polimerler

Introduction

Denture base materials made of polymethylmethacrylate (PMMA) have dominated the market for more than 50 years (1). For denture-wearing patients with allergy susceptibility, hypoallergenic denture base materials provide an alternative to traditional PMMA, lowering the likelihood of adverse responses brought on by lingering methyl methacrylate monomer (MMA) (2,3). Modified methacrylate-based denture base resins had a much lower residual monomer concentration than heat-polymerized PMMA (4,5).

Polyamides are thermoplastic polymers formed through the condensation reaction of a diamine and a dibasic acid (6). PMMA is an amorphous polymer, whereas polyamide is crystalline. Some of the disadvantages of nylon are discoloration, staining, high water absorption and a rough surface after a short time (7,8).

All dental materials must maintain color stability because changes in color are signs of material deterioration or aging (9). Patients may become dissatisfied and incur additional costs for replacement as a result of changes in the color of prosthodontic materials (10).

The majority of prosthetic materials are prone to sorption, a liquid absorption and adsorption process that is influenced by environmental factors (1,11-13). The specimens' color may change due to surface features, microporosity, an excess of residual monomer, overheating or underpressurization during polymerization, or any combination of these factors (14,15).

Despite research on the color stability of acrylic resin denture bases (16,17), there is little data comparing these resins to monomer-free and polyamide resins when submerged in liquids. This *in vitro* study's goal was to determine how frequently ingested liquids including coffee, tea, and coke affected the color stability of PMMA and modified MMA acrylic as well as polyamide denture base materials over time. The first null hypothesis stated that denture base acrylic, conventional PMMA, modified MMA, and polyamide resins would not stain after being immersed in beverages. The second null hypothesis was that surfaces roughness of the tested materials would not effect on color stability.

Materials and Methods

For each material, twenty disk-shaped specimens with a diameter of 10 mm and a height of 2 mm were prepared.

Meliodent, a brand of conventional PMMA resin made by Heraeus Kulzer in Senden, Germany, was mixed using the manufacturer's suggested powder-to-liquid ratio of 35 g to 14 mL. Meliodent was polymerized in a water bath for 90 minutes at 70 °C, followed by 30 minutes at 100 °C.

Two different monomer-free modified MMA (Bre-Crystal, Bredent, Senden, Germany and Acryfree, Perflex, Netanya, Israel) resin specimens were flasked using injection-specific equipment. The polymerization took place in 2-3 minutes at 100 °C in a cartridge that was heated to 260 °C for use in an injection device.

Three different polyamide (Bre-Flex, Bredent, Senden Germany; Flexinylon, Bredent, Senden, Germany; and T Crystal, Perflex, Netanya, Israel) resin specimens were preheated at 222 °C for 15 minutes. The heated and softened resin was injected into the mold in 90 seconds. Each specimen had smooth and rough surfaces after deflasking.

Prior to the color measurements, all specimens were kept in distilled water at 37 °C for 48 hours. A colorimeter (CR 2000; Minolta Inc, Osaka, Japan) was used to measure the color of each specimen at that time (T0).

Following the initial color assessments, specimens were submerged in distilled water as a negative control and three staining solutions (coffee, tea, and coke) as test groups. Five teabags (Lipton Yellow Label Tea; Unilever, Istanbul, Turkey) were dipped into 1,000 mL of heated water to create the tea solution. Twenty g of coffee (Nescafe Classic; Nestle, İstanbul, Turkey) was dissolved in 1,000 mL of boiling distilled water to create the coffee solution (18). Every 30 minutes, both solutions were swirled for 10 seconds until they reached a temperature of 37 °C. Pour 1,000 mL of Coca-Cola (Coca-Cola Co, Çorlu, Turkey) at room temperature into a container to prepare it for coke solution. Distilled water was used as a control group. Every three days, staining solutions were changed. The color of the specimens was once more measured after 1-day (T1), 12-day (T2), and 36-day (T3) soaking periods. Between time intervals, samples were kept in distilled water in a water bath at 37 °C. One day's worth of storage was chosen as

the benchmark period. However, according to the coffee producer, it takes 15 minutes on average to finish one cup of a beverage, and daily coffee consumption among drinkers is 3.2 cups. As a result, one day of storage represented the beverage's consumption over a month (19).

Color changes were described using the Commission Internationale d'Eclairage (CIE) L*a*b* color space. The formula for total color differences is: $\Delta E^*=[(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2]^{½}$ where ΔL*, Δa*, and Δb* are differences in the corresponding L*, a*, and b* values, respectively (20). To measure the color values, a colorimeter (CR 2000; Minolta Inc, Osaka, Japan) was used. Prior to immersion, the initial color values were recorded. Values for color change were also calculated after T1, T2, and T3 periods. The colors of all specimens' smooth and rough surfaces were measured.

The data were transformed to National Bureau of Standards (NBS) units using the equation [NBS units = ΔE*0.92] in order to connect the amount of ΔE* to a clinical environment. Table 1 shows the critical remarks about color differences as expressed by NBS units.

Statistical Analysis

The software program (SPSS Inc; Chicago, IL, USA) was used to compute mean values and standard deviations for each group. The data were statistically evaluated using repeated measure analysis of variance and the Duncan test. Post-hoc tests and Bonferroni adjustments were used to determine whether there was a significant difference within and between subgroups.

Table 1. NBS system of expressing color difference

Critical remarks of color differences	NBS units
Trace	0.0-0.5
Slight	0.5-1.5
Noticeable	1.5-3.0
Appreciable	3.0-6.0
Much	6.0-12.0
Very much	>12.0

NBS: National Bureau of Standards

Results

The results of repeated test all variables (time, denture base materials, surface features, and beverages) were statistically significant (p=0.038), according to ANOVA (Table 2).

Regardless of time or beverage, there was no statistically significant difference between smooth and rough samples (p=0.414). The results of between different variables (surface features, denture base materials and beverages) were not statistically significant (p=0.326) (Table 3).

Figure 1 shows the mean ΔE values of the tested combinations for each immersion time. At the end of T1, T2, and T3 period, Bre-crystal exhibited statistically significant lower color difference (p<0.05).

Figure 2 shows the mean ΔE values of the specimens in beverages for each immersion time (T1, T2 and T3). At the end of T2 period, tea caused statistically significant color change than distiled water (p<0.05). After T1 and T3 periods, beverages did not cause statistically significant color change than distilled water (p>0.05).

Regardless of time, modified MMA (Acryfree) and conventional PMMA (Meliodent) specimens exposed to coke demonstrated statistically significant lower color stability than all others (p<0.05) (Figure 2).

Based on the NBS system, the color changes for all materials after T3 period ranged between "slight" and "much". In the "trace" and "too much" categories, no color change was observed.

Table 2. Within subjects effects of ΔE for denture base resins

Source	df	SS	MS	F	p-value
Time (T)	2	6.934	3.467	2.385	0.093
T x surface (S)	2	4.450	2.225	1.530	0.218
T x material (M)	10	32.266	3.227	2.220	0.016*
T x beverage (B)	6	71.482	11.914	8.195	<0.0001*
T x S x M	10	70.906	7.091	4.878	<0.0001*
T x S x B	6	8.872	1.479	1.017	0.414
T x M x B	30	159.161	5.305	3.650	<0.0001*
T x S x M x B	30	66.977	2.233	1.536	0.038*
Error (time)	384	558.215	1.454		

df: Degrees of freedom, SS: Sum of squares, MS: Mean square
*Statistically significant (p<0.05)

Table 3. Between subjects effects of ΔE for denture base resins					
Source	**df**	**SS**	**MS**	**F**	**p-value**
Surface (S)	1	30.331	30.331	6.811	0.010*
Material (M)	5	907.762	181.552	40.769	<0.0001*
Beverage (B)	3	42.386	14.129	3.173	0.025*
S x M	5	136.358	27.272	6.124	<0.0001*
S x B	3	18.519	6.173	1.386	0.248
M x B	15	210.144	14.010	3.146	<0.0001*
S x M x B	15	75.906	5.060	1.136	0.326
Error	192	855.015	4.453		

df: Degrees of freedom, SS: Sum of squares, MS: Mean square
*Statistically significant (p<0.05)

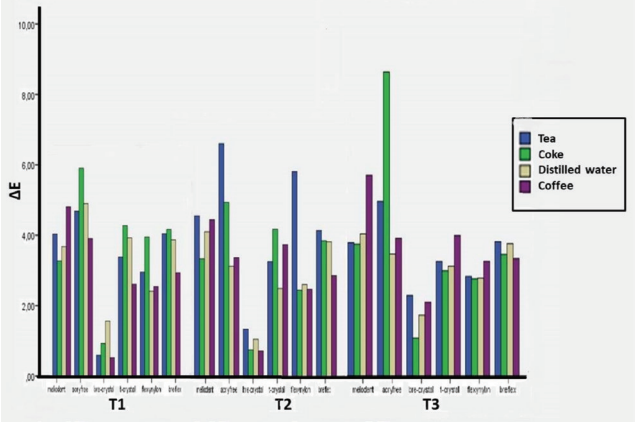

Figure 1. Mean color differences (ΔE) of denture base materials in T1, T2, and T3 immersion periods

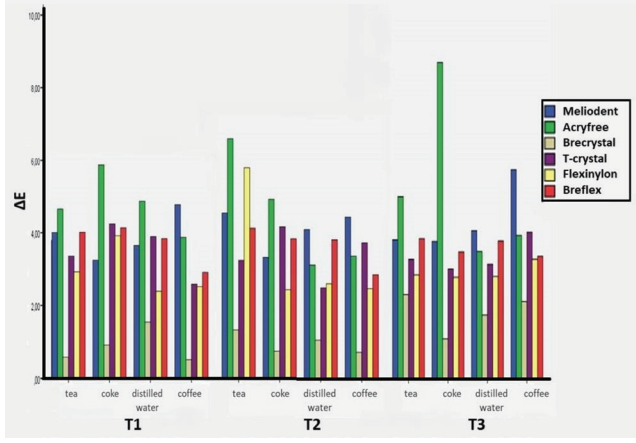

Figure 2. Mean color differences (ΔE) of denture base materials in beverages for T1, T2, and T3 immersion periods

Discussion

In tested denture base specimens at T1 and T3 time intervals, the beverages did not cause a significant difference in color change when compared to distilled water. Because tested denture base materials stained after immersion in tea at T2 time intervals, the first null hypothesis of this study was partially accepted.

There was no statistically significant difference between smooth and rough specimens, regardless of time or beverage. Thus, the second null hypothesis was accepted. The color stability of denture base material is critical for keeping the aesthetic appearance of the removable acrylic prosthesis (16). Although color stability of polished, smooth surfaces is vital for the aesthetic success of the removable dentures, this study considered color change values of both smooth and rough surfaces. The rough surfaces were produced against the plaster surface to replicate the tissue surface in clinical applications. The smooth surfaces were created utilizing the double-sided flask process, which involved polymerizing the materials against the glass surface in the flask. It is not possible to manufacture absolutely smooth surfaces *in vitro* because denture base resins can not be prepared against the glass surface in real clinical conditions. Although the technique of preparing the denture base materials against the glass surface does not fully reflect clinical conditions, it was chosen because it provides gloss surface standardization. Because polyamide-based resins are more difficult to polish than PMMA resins (7,21), the color changes of both smooth and rough surfaces were calculated. In a study examining the color stability, surface roughness, and surface porosity of acrylic resins, it was found that the attributes of surface roughness and color stability were not directly related to one another (15).

Since polyamide denture base materials are hygroscopic, moisture content may fluctuate depending on environmental conditions. Each polyamide type's chemical composition and water absorption are influenced by the frequency of amide groups throughout the chain (8). It is suggested

that the concentration of amide groups in nylon 6 and 66 materials be lowered since the sorbed moisture rises with the concentration of amide groups. Strong hydrogen bonds are established between the amide groups as a results of this formation, the binding of water molecules to these places diminished (22). Kurtulmus et al. (12) found no significant differences in liquid sorption values between different heat-polymerized acrylic and polyamide resin polymerization techniques, however denture base materials with crosslinking agents absorbed less solution than materials without crosslinking agents. Lai et al. (13) investigated the color stability and water absorption of four denture base materials and discovered that PMMA materials had better color stability and lower water absorption, while copolyamide materials had the highest water absorption value and silicone materials had the lowest. On the other hand, when Pfeiffer and Rosenbauer (1) compared the water solubility and water absorption of hypoallergenic and standard PMMA resins, they found that the hypoallergenic denture base materials had water absorption that was at least as high as that of PMMA material.

According to the findings of the current study, modified MMA resin (Bre-Crystal) produced the lowest color difference values. The color stability of the polyamide resins used was slightly better than Meliodent. There were similar ΔE values for polyamide groups across all time intervals, but there was a significant difference between hypoallergenic, MMA-free resins. It can be attributed to differences in composition and processing of this materials.

Staining develops over time as a result of the use of various dyestuffs and beverages, as well as the aging of materials. Coffee, tea, and coke were used as staining materials in the current study, as in previous studies (9,19). After a one-day immersion period, tea, coffee, and coke did not produce a statistically significant color change when compared to distilled water. Similarly, Buyukyilmaz and Ruyter (17) reported that after 96 hours of immersion in coffee and tea solutions, the discoloration values of different denture base materials were the same.

Tea generated a statistically significant color change after 12 days when compared to distiled water. Since Turkey has the largest tea consumption per capita (3.16 kg), dentists and denture-wearing patients should take into this consideration (23).

NBS parameter, which just needs to assess ΔEab values rather than separate L*, a*, and b* values, is useful for color comparison and quality control applications (20,24). For all time intervals, the changes found between 0.36 and 7.16 could be classified as “trace” or “much” using the NBS system that expresses color difference. These results were in line with those of a study that examined the expresses of color difference and utilized two heat-cured denture base acrylics and one nylon denture base resin (11).

One of the limitations of this study was the lack of SEM images of the surface of the samples. In future studies, CIEDE2000, which is the most current formula should be used to evaluate the color stability. Other factors, such as thermal cycling or wear, influence the overall color change (24,25). The lack of such a test environment can be viewed as a limitation and an area for future research.

Conclusion

The following conclusions were reached within the scope of the study:

1. The staining solutions (tea, coffee, and coke) did not cause a significant color change in tested denture base specimens when compared to distilled water at T1 and T3 time intervals.

2. The color stability of the modified MMA resin (Bre-Crystal) was the best at all time intervals.

3. The smoothness or roughness of the surfaces of all tested denture base materials had no effect on color stability.

Ethics

Ethics Committee Approval: This study does not require ethics committee approval.

Informed Consent: This study does not require informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.A., Design: H.A., A.G., Data Collection or Processing: H.A., P.O., Analysis or Interpretation: R.D., Literature Search: G.D.G., A.G., Writing: G.D.G., P.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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Effects of Intracanal Medicaments and Coronal Barrier Materials Used in Regenerative Endodontics on the Fracture Resistance of Simulated Immature Teeth

Rejeneratif Endodontide Kullanılan Kanal İçi Medikamanların ve Koronal Bariyer Materyallerinin Simüle İmmatür Dişlerin Kırılma Direncine Etkisi

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Abstract

Objective: Immature teeth are more susceptible to fracture because of their fragile roots. Intracanal medicaments and coronal filling materials used in regenerative endodontics affect the fracture resistance of immature teeth. This study evaluated the fracture resistance of simulated immature teeth coronally filled with mineral trioxide aggregate (MTA) and EndoSequence (ES) BC Root Repair Material following the intracanal placement of several antibiotic pastes.

Materials and Methods: Sixty maxillary central incisors simulating immature teeth were divided into six randomized groups (n=10/group) according to the type of antibiotic pastes [triple antibiotic paste (TAP; a mixture of metronidazole, ciprofloxacin and minocycline); modified triple antibiotic paste (mTAP: metronidazole, ciprofloxacin and cefaclor); or augmentin] and used coronal barrier materials (MTA; or ES). After 21 days of storage, the antibiotic pastes were removed, and the coronal-barrier materials were placed. The samples were submitted to the fracture tests. The data were analyzed using t-test and one-way ANOVA tests. The significance level was set at $\alpha<0.05$.

Results: Fracture resistance was significantly lower for the mTAP-MTA group than the other MTA groups ($p<0.05$) and for the mTAP-ES group ($p<0.05$). No significant differences were observed for the other pair-wise comparisons ($p>0.05$).

Conclusion: Immature teeth coronally filled with MTA were more prone to fracture than ES after intracanal placement of mTAP. Before coronal MTA filling, the placement of mTAP decreased the fracture resistance of immature teeth compared with other medicaments. The teeth coronally filled with ES presented with similar fracture strength regardless of the application of intracanal medicament.

Keywords: Antibiotics, biomaterials, fracture strength, regenerative endodontics

Öz

Amaç: İmmatür dişler, ince kökleri nedeniyle kırılmaya yatkındır. Rejeneratif endodontide kullanılan kanal içi medikamanlar ve koronal dolgu materyalleri, immatür dişlerin kırılma direncini etkilemektedir. Bu çalışmanın amacı, farklı antibiyotik patların kanal içi uygulaması sonrası mineral trioksit agregat (MTA) ve EndoSequence (ES) BC Root Repair Material ile koronal olarak dolumu yapılmış simüle immatür dişlerin kırılma direncini değerlendirmektir.

Gereç ve Yöntemler: İmmatür dişleri simüle eden altmış adet maksiller santral diş, uygulanan kanal içi antibiyotik patı [üçlü antibiyotik patı (ÜAP: metronidazol, siprofloksasin ve minosiklin); modifiye üçlü antibiyotik patı (mÜAP: Metronidazol, siprofloksasin ve sefaklor); ve augmentin], ve koronal bariyer materyaline göre (MTA ve ES) rastgele altı gruba ayrıldı (n=10/grup). Antibiyotik patları, 21 gün sonra kanaldan uzaklaştırıldı ve koronal bariyer materyalleri yerleştirildi. Numuneler kırılma testine tabi tutuldu. Veriler t-testi ve tek yönlü ANOVA testleri kullanılarak analiz edildi. Anlamlılık düzeyi $\alpha<0,05$ olarak belirlendi.

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Bulgular: Kırılma direnci mTAP-MTA grubunda, diğer MTA gruplarına göre ($p<0,05$) ve mTAP-ES grubuna göre ($p<0,05$) anlamlı derecede düşüktü. Diğer ikili karşılaştırmalar arasında anlamlı bir farklılık gözlenmedi ($p>0,05$).

Sonuç: Rejeneratif endodontik tedavi prosedüründe, mTAP'nin kanal içi uygulamasından sonra, koronal olarak MTA ile doldurulmuş immatur dişler, ES ile doldurulmuş dişlere göre kırılmaya daha yatkındı. Koronal MTA dolgusu öncesi kök kanallarına mTAP yerleştirilmesi, olgunlaşmamış kök anatomisi taklit edilmiş dişlerde diğer medikamanlara kıyasla kırılma direncini azalttı. Koronal olarak ES ile doldurulmuş dişler, uygulanan kanal içi medikamana bağlı olmaksızın benzer kırılma direnci sergiledi.

Anahtar Kelimeler: Antibiyotik, biyomateryaller, kırılma direnci, rejeneratif endodonti

Introduction

Endodontic treatment of non-vital immature teeth is challanging due to their wide-open apices and thin root canal walls. The loss of tooth structure diminishes fracture strength against traumatic and excessive occlusal forces (1). Regenerative endodontic treatment (RET) may be used to replace functional pulpal tissue and eventually maintain root development by increasing the lengths and widths of immature roots. RET is a biology-based approach that contains three primary elements of tissue engineering: stem cells, growth factors, and scaffolds (2).

The clinical steps of the RET procedure may be summarized as follows: minimal/no preparation and disinfection of the root canals, intracanal bleeding formation, and coronal sealing (3). Disinfection of the root canals is mostly achieved using intracanal medicaments in the RET procedure (3). Therefore in regeneration-based approaches, calcium hydroxide and triple antibiotic paste (TAP; a mixture of metronidazole, ciprofloxacin and minocycline) are generally preferred as intracanal dressing materials (4). Since calcium hydroxide increases the risk of future cervical root fractures by increasing the brittleness of root dentin, antibiotic pastes appear to be the preferred choice (5). Several antibiotic mixtures, such as modified triple antibiotic paste (mTAP: metronidazole, ciprofloxacin and cefaclor), double antibiotic paste (DAP: metronidazole, ciprofloxacin) and augmentin have also been recommended for this purpose (6). The impact of antibiotic pastes on chemical and physical compositions of dentin has been proven in previous studies (7). The long-term application of intracanal medicament has a negative effect on dentin structure and generally results in a reduction of fracture resistance (8). However, the possible negative effects of antibiotic pastes have not yet been clarified yet.

During the RET procedure, below the cemento-enamel junction, a 2 mm thickness of coronal filling material is applied directly onto the blood clot, which consists of stem cells (3,9). Mineral trioxide aggregate (MTA) is the most commonly used material for providing intra-orifice barriers because of its perfect sealing ability and stimulation effect on stem cells (4,9). However, even with white MTA some degree of tooth discoloration has been reported (10). A calcium silicate-based material, EndoSequence (ES) BC Root Repair Material (Brasseler, Savannah, GA, USA), has stood out with stem cell differentiation capacity and has caused less tooth discoloration in RET procedures (9,11).

The effect of MTA and ES placements have already been investigated with respect to the fracture strength of immature teeth (12,13). However, in contrast to the recommendations of European Society of Endodontology (ESE) that "coronal barrier material should be placed 2 mm below the cement-enamel junction" (3), the root canals were completely filled in these aforementioned studies (12,13). A review of the literature reveals that, no study has evaluated fracture resistance effects in simulated immature teeth treated with a combination of several antibiotic pastes and coronal sealing materials. Therefore, this study aimed to evaluate the fracture resistance of simulated immature teeth filled with MTA and ES as coronal barrier materials following the intracanal placement of TAP, mTAP, and augmentin pastes. The null hypothesis was that no difference would be detected between coronal sealing materials and among antibiotic pastes with respect to the fracture resistance of immature teeth.

Materials and Methods

The study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University (decision no: 51, date: 27.12.2019). Sixty non-decayed maxillary central incisor teeth that extracted for orthodontic or periodontal reasons were selected. Single-rooted upper centrals with one root canal were included in this study also it was confirmed radiographically and visually that there were no cracks or resorption in the teeth.

Sample Preparation

To simulate immature teeth, the teeth's apical parts were cut using a diamond disc to standardize the remaining root length at 9 mm. Endodontic access cavities were prepared using diamond burs. The root canals were prepared with #1 to #6 Peeso reamer drills and carbid burs by passing beyond apex to obtain a 2.1 mm internal diameter for simulating the Cvek's stage #2 of root development (14,15). Between each instrument change, 2 mL of 1.5% sodium hypochlorite (NaOCl, Werax, İzmir, Turkey) was used for irrigation. Finally, the root canals were irrigated with NaOCl (1.5%, 20 mL, 5 min), followed by distilled water (20 mL, 5 min) and ethylenediaminetetraacetic acid (EDTA; Werax, İzmir, Turkey) (17%, 20 mL, 5 min) solutions. The root canals were dried with paper points and then the apical parts of the teeth were sealed with composite resin. After that, the samples were divided into six groups according to type of antibiotic

paste and type of intra-orifice filling material (n=10), as presented in Table 1.

RET Procedures

The antibiotic pastes used in this study were prepared as follows:

TAP: Metronidazole (Eczacıbaşı, İstanbul, Turkey), ciprofloxacin (Biofarma, İstanbul, Turkey), and minocycline (Ratiopharm, Ulm, Germany) were mixed to at a ratio of 1:1:1.

mTAP: Metronidazole (Eczacıbaşı, İstanbul, Turkey), ciprofloxacin (Biofarma, İstanbul, Turkey), and cefaclor (Sanovel, İstanbul, Turkey) was mixed to at a ratio of 1:1:1.

Augmentin: The antibiotic paste was made using augmentin (GlaxoSmithKline, İstanbul, Turkey).

All antibiotic pastes were prepared by mixing the powders with distilled water (powder-to-liquid ratio 1 mg: 1 mL). The antibiotic pastes were placed into the root canals with the aid of a Lentulo spiral. The access cavities were then temporarily sealed using CavitG (3M ESPE, Seefeld, Germany). The teeth were stored at 37 °C under 100% humidity for 21 days. Removal of the antibiotic pastes was performed using EDTA (17%, 20 mL, 5 min) and distilled water (5 mL) rinse (3). The root canals were then dried with paper points.

The coronal thirds of the root canals were obturated below the cemento-enamel junction (with 2 mm thickness) using the MTA (ProRoot MTA; Dentsply Sirona, Ontario, Canada) and ES (Brasseler; Savannah, Georgia, USA), in accordance with the manufacturer's instructions. The teeth were restored with a light-cured composite after the 12 hour setting period of both MTA and ES. The teeth were incubated at 37 °C and 100% humidity for 7 days until measuring their resistance for fracture.

Table 1. Experimental groups according to antibiotic paste and barrier material application

Groups (n=10)	Antibiotic paste	Barrier material
I	TAP	MTA
II	TAP	ES
III	mTAP	MTA
IV	mTAP	ES
V	Augmentin	MTA
IV	Augmentin	ES

TAP: Triple antibiotic paste, mTAP: Modified triple antibiotic paste, MTA: Mineral trioxide aggregate, ES: Endosequence root repair material

Fracture Strength Evaluation

The roots were embedded at the level of cemento-enamel junction into cylindrical acrylic resin blocks. The fracture strength was tested using a universal testing machine (Lloyd, Lloyd Instruments Ltd, West Sussex, United Kingdom) and the compression loads were applied at a crosshead speed of 1 mm/min. The occlusal load was applied to the cingulum at an angle of 135 degrees. The maximum force required to fracture was recorded in Newtons.

Statistical Analysis

Descriptive and analytical statistics of the data were analyzed using SPSS software (ver. 21; Chicago, IL, USA) at the significance level of α=0.05. Normal distribution of the data was evaluated using the Shapiro-Wilk test. Statistical analysis was carried out using one-way ANOVA test followed by Tukey's post hoc test for multiple comparisons. A t-test was used to evaluate statistical differences between the means of the two groups.

Results

Table 2 represents the mean force values that generated fracture in the experimental groups.

Analysis of Antibiotic Pastes

No significant difference was observed among the groups in which ES repair material was used as coronal plug in terms of fracture strength reduction triggered by different antibiotic pastes ($p>0.05$). In MTA filling groups, intracanal placement of mTAP exhibited lower fracture resistance compared to TAP and augmentin, while no significant difference was observed between TAP and augmentin ($p>0.05$).

Analysis of Coronal Barrier Materials

Coronal MTA filling caused statistically lower fracture resistance when compared to ES filling after the intracanal

Table 2. Mean and standard deviation values (N) of fracture strength for the experimental groups (n=10)

Antibiotic pastes	MTA		ES		t value	P
	Groups	Mean ± SD	Groups	Mean ± SD		
TAP	I	287.19±38.27[a]	II	223.1±49.25[a]	1.027	0.318
mTAP	III	113.31±15.63[b]	IV	282.49±41.74[a]	3.796	0.003*
Augmentin	V	278.54±36.9[a]	VI	237.41±43.53[a]	0.721	0.480

SD: Standard deviation. TAP: Triple antibiotic paste, mTAP: Modified triple antibiotic paste, MTA: Mineral trioxide aggregate, ES: Endosequence root repair material. Different lowercases mean statistically significant differences between the groups within the same column ($p<0.05$, ANOVA; Tukey)

placement of mTAP ($p<0.05$). However, no significant difference was observed between MTA and ES fillings ($p<0.05$), when TAP or augmentin was used as intracanal medicament.

Discussion

This study investigated the effects of MTA and ES on the fracture resistance of immature teeth following intracanal medicament placement of TAP, mTAP, and augmentin. The fracture resistance scores was lower for the mTAP-MTA group than for the other MTA groups and also lower than the mTAP-ES group. Therefore, the null hypothesis of the present study could not be accepted.

Prior to the blood clot formation, a final irrigation with 17% EDTA is advised as it stimulates growth factor release and stem cell formation in RET procedures (16). Therefore, in the present study, the root canal medicaments were removed using 17% EDTA. The irrigation procedure was performed according to the RET protocol of ESE to mimic possible structural changes in the dentin. It has been claimed that prolonged exposure of root canals to antibiotic pastes diminishes the fracture resistance of the immature teeth depending upon the demineralization of dentin (17).

Several studies evaluated MTA and other barrier materials with respect to their influence on fracture resistance of immature teeth filled in two scenarios one with using repair materials as apical plugs (18) and other with using as the obturation material of the entire root canal system (12,13). A review of the existing literature reveals that one study evaluated the fracture resistance of MTA as a coronal filling of 3 mm thickness below the cemento-enamel junction (19). In contrast to our study which MTA was used in the coronal parts of the roots, the roots were apically filled with MTA and restored with fiber-posts were evaluated in that study. Based on our research, no other study has compared the effect of MTA and other intra-orifice barrier materials on the fracture resistance of immature teeth when performed exactly as recommended by ESE (with 2 mm thickness just below the cemento-enamel junction) (3). In this regard, the present study compared, the fracture strength of teeth with MTA coronal plug and teeth with ES coronal plug with 2 mm thickness just below the cement-enamel junction. The results of this study showed that MTA and ES provided similar fracture resistance following the application of TAP and augmentin, while ES was superior after mTAP placement. An earlier study has compared simulated immature teeth which were filled with MTA, ES, and BioAggregate with respect to fracture resistance (13) and found that fracture resistance scores of ES was superior to MTA. Contrary to our study, in the aforementioned study (13), the root canals were completely filled with repair material and no medicament was applied to the root canals, and were used different brand of MTA than in our present study.

These changes in physical and chemical composition of the root dentin the could affect the fracture resistance of the immature teeth that are already prone to fracture (20). In previous studies, the intracanal usage of TAP, DAP, and calcium hydroxide have previously been associated with collogen degradation from dentin (17) and it has been reported to decrease on the fracture resistance of immature teeth (20). In this study, in MTA groups, mTAP reduced the fracture strength of the teeth compared to the TAP and augmentin. The medicament on dentin walls could only be removed through 17% EDTA irrigation, as minimal preparation is advised. Therefore, antibiotic pastes could not be completely eliminated from the dentin walls (21). The coronal barrier material reacts chemically with the dentin (22) and probably with the residual medicaments. It has been found that mTAP has induced a higher increase in pH than TAP by raising the Ca/P ratio on the dentin surface (23). It was also observed that MTA caused a higher pH value than ES did (24). The additional effect between MTA and mTAP might have created a more alkaline environment compared to other groups. It has been determined that alkaline pH can make the root structure more susceptible to fracture (25). The lowest fracture resistance value observed in the mTAP-MTA group may be related to alkaline pH. Further studies are required to evaluate the reaction between antibiotic pastes and coronal sealing materials.

Conclusion

The immature teeth coronally filled with MTA were more prone to fracture compared to ES after intracanal placement of mTAP. Prior to coronal MTA filling, placement of mTAP decreased the fracture resistance of immature teeth when compared to other medicaments. The teeth coronally filled with ES presented similar fracture strength regardless of the applied intracanal medicament.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Yıldırım Beyazıt University (decision no: 51, date: 27.12.2019).

Informed Consent: This study does not require informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S., S.İ.Y., M.A., Concept: E.S., Design: E.S., Data Collection or Processing: E.S., S.İ.Y., M.A., Analysis or Interpretation: E.S., S.İ.Y., Literature Search: E.S., Writing: E.S.

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Effect of Chitosan and EDTA Solutions on Bond Strength of Two Different Calcium Silicate Based Materials

Kitosan ve EDTA Solüsyonlarının İki Farklı Kalsiyum Silikat Esaslı Malzemenin Bağlanma Dayanımına Etkisi

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Abstract

Objective: The aim of the present study was to evaluate the potential of using chitosan-based chelating agents to improve the bond strength of mineral trioxide aggregate (MTA) Angelus (Londrina, PR, Brazil) or MTA Repair high plasticity (Londrina, PR, Brazil).

Materials and Methods: A total of 60 dentine discs were obtained from 15 freshly extracted human maxillary central incisors. Two canal-like holes were drilled and the disks were divided into four groups, as following; group 1: chitosan solution with acetic acid; group 2: chitosan solution with lactic acid; group 3: 17% ethylenediaminetetraacetic acid; and group 4: distilled water. Discs were subjected to the tested chelating solution for smear layer removal for 3 min. The two holes of the same dentine discs were each randomly filled with one of the tested materials. The push-out test was performed and data were analyzed using 2-way analysis of variance test with a 5% significance level.

Results: No significant differences were observed for the type of tested material (p=0.153) and the interaction between tested material and solution (p=0.922); however, there was a significant difference among chelating agents (p=0.001).

Conclusion: Both materials showed similar bond strength regardless of the a chelating agent was used or not. All chelating agents significantly decreased the push-out strength of both materials, except for the chitosan solution prepared with acetic acid.

Keywords: Chelating agents, ethylenediaminetetraacetic acid, chitosan, mineral trioxide aggregate, dental bonding

Öz

Amaç: Bu çalışmanın amacı, mineral trioksit aggregat (MTA) Angelus (Londrina, PR, Brezilya) veya MTA Repair high plasticity (Londrina, PR, Brezilya) materyalinin dentine olan bağlanma dayanımını artırmak için kitosan bazlı şelatlama ajanlarının kullanım potansiyelini değerlendirmektir.

Gereç ve Yöntemler: On beş adet yeni çekilmiş maksiller santral kesici dişinden toplam 60 adet dentin diski elde edildi, dentin disklerinde iki adet kanala benzer delik açıldı ve dört gruba ayrıldı; grup 1: asetik asitle hazırlanan kitosan solüsyonu; grup 2: laktik asitle hazırlanan kitosan solüsyonu; grup 3: %17 etilen diamin tetra asetik asit; ve 4. grup: distile su. Diskler 3 dakika süreyle smear tabakasının uzaklaştırılması için test edilen şelatlama solüsyonuna tabi tutuldu. Aynı dentin diskinin iki deliğinden her biri, test edilen malzemelerden biri ile rastgele dolduruldu. Push-out testi gerçekleştirildi ve veriler %5 anlamlılık düzeyinde 2 yönlü varyans analizi testi kullanılarak analiz edildi.

Bulgular: Test edilen materyalin tipi (p=0,153) ve test edilen materyal ile çözelti arasındaki etkileşim (p=0,922) açısından önemli bir farklılık gözlenmedi; ancak şelatlama solüsyonları arasında anlamlı farklılık vardı (p=0,001).

Sonuç: Her iki materyal şelatlama solüsyonu kullanılıp kullanılmadığına bakılmaksızın benzer bağlanma dayanımı gösterdi. Asetik asit ile hazırlanan kitosan solüsyonu haricinde tüm şelatlama solüsyonları her iki materyalin dentine olan bağlanma dayanımını önemli ölçüde azaltmıştır.

Anahtar Kelimeler: Şelatör ajanlar, etilendiamintetraasetik asit, kitosan, mineral trioksid agregat, diş yapıştırma

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Introduction

During the root canal instrumentation, a smear layer containing organic and inorganic materials is formed. Removal of this layer may positively affect the root canal disinfection and the adaptation of obturation materials (1). Various chemicals have been investigated to remove the smear layer. The most common chemical Ethylenediaminetetraacetic acid (EDTA) chelate calcium ions in dentine and forms soluble Ca-EDTA complex. However, EDTA has cytotoxic potential and is considered as an environmental pollutant (2).

Chitosan is a natural aminopolysaccaride. Many organic acids have been recently suggested as a solvent to form chitosan conjugates. One of those acids, lactic acid has been suggested as a chelating agent in endodontics and chitosan dispersion prepared with lactic acid has been associated with low cytotoxicity, high biocompatibility, hydrophilicity and great antibacterial properties (3).

Calcium silicate based cements can be considered as the gold standard material for several clinical procedures in endodontics. One of these cements, mineral trioxide aggregate (MTA) Angelus (MTA-Ang; Londrina, Brazil) is composed of 80% Portland cement and 20% bismuth oxide. MTA Repair high plasticity (MTA-HP; Londrina, Brazil) has been introduced with high-plasticity and improved physical properties compared to MTA Angelus (4).

Bond strength has been defined as a measure of frictional sliding that can be conventionally tested using the push-out test method and influenced by root canal chelating agents leading to changes in the content of dentine and the physicochemical properties of calcium silicate-based materials (5,6). Hereby, it is recommended for flushing the area with copious amounts of distilled water to remove chelating agents completely (6). However, contact of calcium silicate based materials with chelating agents may be unavoidable for some endodontic treatments such as regenerative procedures in which chelating agents are used as final irritant to release growth factors from dentine (6). In several studies, the adhesive properties of calcium silicate-based materials have been assessed after irrigation with various solutions (7,8). Up to now, only one study has been previously investigate the effect of chitosan based chelating agents on bond strength of calcium silicate based materials (9). We conducted this study to test two null hypotheses: (i) there is no differences in the bond strength between MTA-Ang and MTA-HP, and (ii) the chelating agents do not affect the push-out performance of the MTA-Ang and MTA-HP.

Materials and Methods

Sample Selection and Preparation

The study was realized in accordance with Declaration of Helsinki and approval was obtained through the Local Ethics Committee at Ankara University (decision no: 36290600/02, date: 17.01.2020). Based on a previous study with effect size of 0.74 (10), a total of 48 disc samples were found to be necessary. The study involved 15 freshly extracted human maxillary mature central incisors without visible sign of root fracture, caries, or resorption. Teeth were embedded in cold cure acrylic (Meliodent, UK). The coronal and apical segments of each tooth were removed to leave 10 mm long middle third of root. Four horizontal dentine discs (1±0.1 mm thick) in the middle third were created using a low-speed saw. A total of 60 dentine discs (n=15 per group) were randomly divided into four groups according to the type of irrigation solution, as following; group 1: chitosan solution with acetic acid; group 2: chitosan solution with lactic acid; group 3: 17% EDTA; and, group 4 (control group): distilled water. Two canal like holes perpendicularly to the surface of each dentine disc were prepared with a 0.8 mm cylindrical carbide bur, maintaining a minimum distance of 0.5-1 mm between the holes, external root surface and inner root canal wall. Dentine discs were immersed in a 2.5% sodium hypochlorite (NaOCl) for 15 minutes and then, each dentine disc from the same tooth was subjected to the tested chelating solution for 3 minutes. For preparation of the chitosan dispersion with acetic acid (pH=2.39), 0.2 g of chitosan was diluted in 100 mL of 1% acetic acid, and stirred using a magnetic stirrer for 2 h. For preparation of the chitosan dispersion with lactic acid (pH=2,186), 0.2 g of chitosan was diluted in 100 mL of 1% lactic acid, and stirred using a magnetic stirrer for 2 h. All dentine discs were flushed with distilled water as the last irrigant for 1 minute and then dried with absorbent paper. The two holes of the same dentine disc were each randomly filled with one of the tested calcium silicate based materials: MTA-Ang or MTA-HP. All tested materials were mixed according to the manufacturers' instructions, placed into the holes using a carrier and condensed with hand pluggers. The dentine discs contacted with gauze moistened (pH 7.2) were kept at 37 °C for 7 days.

The push-out test was performed by an operator who is blinded to the experimental groups using a universal testing machine (Lloyd LRX; Lloyd Instruments Ltd., UK). A plunger tip of 0.6 mm diameter was used in a coronal-apical direction at a crosshead speed of 0.5 mm/min until dislocation. The adhesion surface area was determined through the following formula: $2\pi r$ X h. (r: radius of canal-like hole; h: height of the disc). Push-out bond strength (MPa) = maximum force (N)/adhesion surface area (mm^2).

Fractographic Analysis

All dentine discs were examined under a stereomicroscope at 40x magnification to assess mode of bond failure which were classified as follows: (i) adhesive failure occurred at the material-dentine interface, (ii) cohesive failure within the tested material and (iii) mixed failure.

Statistical Analysis

The data were evaluated with two-way analysis of variance and Tukey's post hoc test by using SPSS 20.0 software (IBM Corp, NY) to determine the effect of chelating solution,

type of tested material and their interaction on push-out strength. The level of statistical significance was set at $p<0.05$.

Results

Two-way analysis revealed a significant difference for the type of solution (p=0.001); however, no significant differences were observed for the type of tested material (p=0.153) and the interaction between tested material and solution (p=0.922). MTA-HP group had slightly higher push-out strength values when compared to MTA-Ang group ($p>0.05$). Regardless of the type of the material used, significantly higher push-out values were obtained from group 4 (discs irrigated with distilled water; no chelating agent), compared with group 2 (discs irrigated with chitosan solution prepared with lactic acid) (Tukey, p=0.000) and group 3 (discs irrigated with EDTA) (Tukey, p=0.012). There was no statistically significant difference between group 1 and group 2 (p=0.21), group 1 and group 3 (p=0.77), group 1 and group 4 (p=0.145), group 2 and group 3 (p=0.754). Group 2 showed the least push-out bond strength. The percentages of the failure modes of the samples were presented in Table 1. Mixed failures were the most observed (Figure 1).

Discussion

This study was designed to assess whether the use of different chelating agents affect the bond strength of two different calcium silicate based materials. According to the results, first null hypothesis was accepted. All chelating agents were associated with a significant decrease in bond strength of tested materials except for chitosan solution prepared with acetic acid, necessitating the partially accepted of the second null hypothesis.

The present study utilized "intra-tooth model" for sample preparation. This model involves providing a horizontal or longitudinal dentine slice from a tooth and creating artificial canal-like holes in the same dentine slice in order to minimize the experimental confounding factors such as differences in root canal anatomy, tooth age, storage time, distribution of sclerotic dentine, and micro-hardness (10,11). Thus, a more reliable sample baseline could be established to make fair comparisons among materials and/or irrigation solutions (11).

The differences between push-out bond strength values of MTA-Ang and MTA-HP for all irrigation regimens were not statistically significant. This result can be attributed to the similarity of their chemical compositions. The only differences of MTA-HP from MTA-Ang are the addition of an organic plasticizer to its liquid and containing calcium tungstate as a radiopacifier. Addition of calcium tungstate instead of bismuth oxide as radiopacifier to calcium silicate based cements has no significant effect on physicochemical properties such as calcium ion release, solubility and pH; however, it associated with less discoloration potential on dental structures (12,13). Unlike the present results, Silva et al. (14) found significantly higher push-out bond strength values for MTA-HP when compared to MTA-Ang. Despite using push-out model similar to those utilized in the present study, there was variability in the irrigation sequence. The authors immersed dentine discs into the NaOCl after irrigation with EDTA. However, in our study, dentine discs were subjected to only distilled water after using chelating agents to eliminate possible effects of NaOCl on hydration process of MTA and organic structure of dentine. Because,

Table 1. Mean push-out bond strength values with standard deviations and failure modes of each material for each group

Groups (Solution)	N	Material	Mean (MPa)	Std. Deviation	Failure modes, % (A/C/M)
Group 1 (Chitosan dispersion mixed with asetic acid)	15	MTA Angelus	4.257	1.677	27/13/60
	15	MTA-HP Repair	4.722	1.953	27/7/67
	30	Total	4.49	1.59900	27/10/63
Group 2 (Chitosan dispersion mixed with lactic acid)	15	MTA Angelus	3.482	1.561	60/0/40
	15	MTA-HP Repair	3.635	1.953	47/0/53
	30	Total	3.5592	1.73897	53/0/47
Group 3 (EDTA)	15	MTA Angelus	3.625	1.766	27/7/67
	15	MTA-HP Repair	4.437	2.228	40/7/53
	30	Total	4.0313	2.01847	33/7/60
Group 4 (Distilled water)	15	MTA Angelus	5.259	1.578	27/13/60
	15	MTA-HP Repair	5.7613	2.258	40/7/53
	30	Total	5.5103	1.93152	33/10/57

EDTA: Ethylenediaminetetraacetic acid, MTA: Mineral trioxide aggregate, MPa: Mycophenolic acid, Std.: Standard

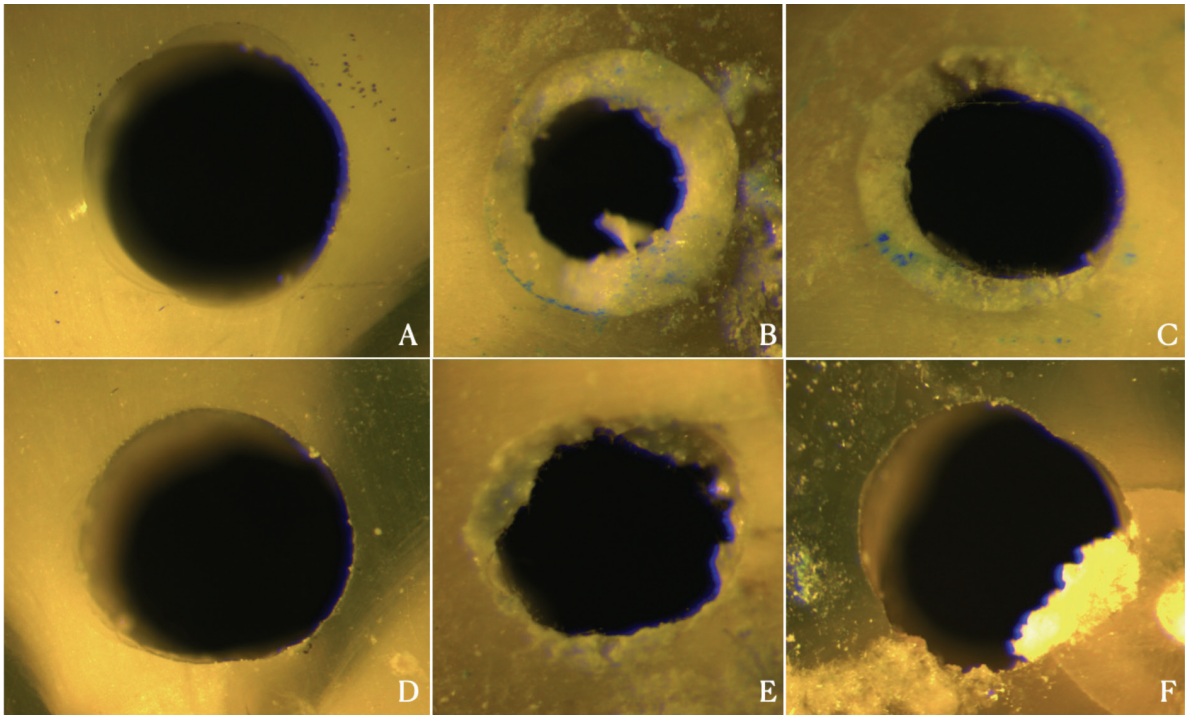

Figure 1. Representative stereomicroscopic images of the mode of bond failures. (A) Adhesive, (B) cohesive, and (C) mixed within MTA Angelus. (D) Adhesive, (E) cohesive, and (F) mixed within MTA Repair HP

MTA: Mineral trioxide aggregate, HP: High plasticity

NaOCl can alter the physical properties of MTA decreasing the portlandite peaks during the hydration and interact with bismuth oxide which forms a part of MTA (8,15). NaOCl can also lead to degrade the collagen fibrils before deposition of hydroxyapatite or carbonated apatite, which are the main components of biomineralization of MTA (16,17).

Fractographic analysis revealed that bond failures for MTA-Ang and MTA-HP were predominantly mixed type of failure followed by adhesive type of failure. The adhesive type of failure could be more observed as the bond strength decreased and this was corroborative the present push-out results. This mixed type of failure indicated that both materials generally presented cohesive and adhesive type of failures at the same time. Several factors such as storage time and particle size of the material were suggested as detrimental factors to determine the mode of bond failure during fractographic investigation. A smaller particle size and longer storage time have been associated with higher bond strength (9,16). However, the mean particle size of the MTA-HP and MTA-Ang was reported to be 11.20 μm and 15.48 μm, respectively, which are greater than the mean tubule diameter of root dentine (2.65-2.90 μm) (18,19). For this reason, the biomineralization capacity of both materials can be considered as a superior factor instead of their infiltration properties via their small particles in terms of attachment to dentin.

All chelating agents used in the present study showed similar effect on bond strength of MTA-Ang and MTA-HP. Similar to a previous study in which use of different chelating agents resulted in no alteration on bond strength of MTA, but lower push-out values were obtained compared to control group (8). Although, distilled water was used as a final rinse after all irrigation protocol to remove chelating solutions from canal-like holes, bond strength of the tested materials was varied according to the type of irrigation solution used. This result can be attributed to presence of trace amount of chelating agent on the dentinal walls or within the dentinal tubules. Additionally, particles of chitosan can deposit on the surface and predominantly within the dentinal tubules, presumably as a result of its highly charged molecular structure (9). Ozlek et al.'s (9) study has suggested that residue of chitosan particles may affect push-out bond strength of mineral trioxide aggregate-resin hybrid root canal sealer.

The hydration mechanism of MTA involves two stages: dissolution of MTA powder with releasing calcium ions into the environment and then, precipitation of the hydrated products. The use of acids during this process could disturb precipitation and crystallization of the hydrated compounds while chelating calcium ions released from MTA (6). Acidic pH could decrease its microhardness and bond strength to root dentine since the acids such as EDTA chelates calcium ions released from MTA (14). All chelating agents used in the present study had a pH level ranged from acidic to neutral and therefore both materials showed higher bond strength in dentine discs irrigated with distilled water solely.

Previous studies have been showed that the capacity of chitosan dispersions to remove calcium ions and smear layer from root canals as efficiently as EDTA is attributed to properties of chitosan and not the contribution of solvent (20). However, use of different solvents may have an effect on physicochemical properties of chitosan dispersions. In a study conducted by Soares et al. (21), chitosan dispersions were prepared with different acids such as lactic acid and acetic acid. Similar to our findings, chitosan dispersion prepared with lactic acid had lower pH level than those prepared with acetic acid (21). This minor change in pH levels of dispersions could be related to the lower push out values obtained from group 2 (chitosan mixed with lactic acid) in comparison with group 1 (chitosan mixed with acetic acid), despite that was not statistically significant. Thus, it could be suggested that the use of different acids in chitosan dispersions would not cause any change in terms of push-out values of tested materials. Additionally, acetic acid and lactic acid were not tested solely, because these solutions are not much preferred clinically.

From the clinical point of view, effect of the chelating agents on the long-term prognosis of endodontic treatments is still unknown, because the factors related to success cannot be isolated and various etiological factors play essential roles in development of post-operative apical pathology. Moreover, from the mechanical point of view, an endodontic material should have good retention properties under static conditions and during masticatory function. However, there are conflicting results regarding whether the smear layer should be removed or not for better mechanical retention (1). Especially for calcium silicate based cements material's adhesion to root dentine occurs as result of biomineralization through formation of tag-like structures into dentinal tubules and this process can be affected by environmental condition such as pH (6). In use of chelating agents, its possible effects on treatment outcome, physicochemical properties of material and material-dentine interactions should be considered. Rather than limiting the use of chelating agents, more studies need to be conducted seeking for alternative ways to buffer their relatively negative effects.

Conclusions

Both materials showed similar bond strength whether chelating agent was used or not. All chelating agents significantly decreased the push-out strength of both materials except for chitosan solution with acetic acid. The effect of chitosan dispersion prepared with lactic acid on push-out bond strength of both materials tested was similar to that of chitosan dispersion prepared with acetic acid. However, other materials can be effected differently by the irrigation sequence and type of irrigation solution and thus, further studies should assess the interaction of other materials with dentine irrigated with chitosan dispersions and characterize their effects on the tested materials.

Ethics

Ethics Committee Approval: The study was realized in accordance with Declaration of Helsinki and approval was obtained through the Local Ethics Committee at Ankara University (decision no: 36290600/02, date: 17.01.2020).

Informed Consent: This study does not require informed consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: C.K., K.G., N.D.K., Design: C.K., K.G., N.D.K., Data Collection or Processing: C.K., K.G., N.D.K., Analysis or Interpretation: C.K., K.G., Literature Search: C.K., Writing: C.K., K.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Effects of Intracanal Medicaments on the Measurement Accuracy of Four Apex Locators: An *In Vitro* Study

Kanal İçi İlaçların Dört Apeks Bulucunun Ölçüm Doğruluğu Üzerindeki Etkileri: *In Vitro* Çalışma

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Abstract

Objective: This study aimed to examine the effect of various intracanal medicaments on the precision of four electronic apex locators (EALs).

Materials and Methods: This study comprised 160 maxillary central incisors. After root canal preparation, a 25-K file was carefully introduced into the root canal until it was perceptible through the apex, and 0.5 mm was subtracted from this amount to determine the actual length. Samples were divided into four groups: calcium hydroxide, double antibiotic paste, triple antibiotic paste, and the control groups. Intracanal medications were removed with EDTA ten days later, and electronic measurements were performed. Chi-square (χ^2) test was used to assess the precision of EALs within the margins of ±0.5 and ±1 mm (α=0.05).

Results: The accuracies of the four EALs did not vary significantly for different intracanal drugs within the bounds of ±0.5 and ±1 mm (χ^2 tests, p>0.05).

Conclusion: The EALs used in this study obtained reliable readings of working length in the context of varying intracanal medications.

Keywords: Calcium hydroxide, antibiotics, root canal medicaments, electronic apex locator

Öz

Amaç: Bu çalışma, çeşitli kanal içi ilaçların dört elektronik apeks bulucunun (EAB) çalışma boyu ölçüm kesinliği üzerindeki etkisini incelemeyi amaçladı.

Gereç ve Yöntemler: Bu çalışma toplam 160 üst orta kesici dişi içermektedir. Kök kanal preparasyonundan sonra, bir 25 numara boyutunda K-tipi eğe kök kanalına yerleştirilerek apeksten algılanıncaya kadar dikkatli bir şekilde ilerletildi ve ardından bu değerden 0,5 mm çıkarılarak gerçek uzunluk belirlendi. Örnekler kalsiyum hidroksit, ikili antibiyotik patı, üçlü antibiyotik patı ve kontrol grubu olmak üzere dört gruba ayrıldı. Kanal içi ilaçlar 10 gün sonra EDTA ile çıkarıldı ve elektronik ölçümler yapıldı. EAB'lerin doğruluklarını ±0,5 ve ±1 mm (α=0.05) hata payı içinde değerlendirmek için ki-kare (χ^2) testi kullanıldı.

Bulgular: Farklı kanal içi ilaç grupları için dört EAB'nin doğruluklarında ±0,5 ve ±1 mm tolerans sınırları içerisinde önemli ölçüde değişiklik tespit edilmedi (χ^2 testleri, p>0,05).

Sonuç: Bu çalışmada kullanılan EAB'ler, farklı kanal içi ilaçların varlığında güvenilir çalışma uzunluğu ölçümleri sağlamıştır.

Anahtar Kelimeler: Kalsiyum hidroksit, antibiyotikler, kök kanal medikamanları, elektronik apeks bulucu

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Introduction

Achieving the proper working length which is an important stage of the procedure (1), is vital for a successful root canal treatment (RCT). Since there are concerns that many factors may affect this measurement, the influence of numerous clinical factors on the precision of electronic apex locators (EALs), such as coronal enlargement (2), diameter of the apical foramen (3), irrigation solutions (4), and intracanal medicaments (5,6), have been investigated by many researchers.

Complex root canal anatomy and the bacteria behind persistent periapical lesions can be especially difficult to clean and disinfect from the root canal system; such conditions may require using medications between RCT sessions (7). The high pH of $Ca(OH)_2$ makes it the optimal intracanal medicament for RCT (8). As alternative intracanal drugs; triple antibiotic paste (TAP) is prepared by mixing ciprofloxacin, metronidazole, and minocycline antibiotics in equal proportions (1:1:1) (8), and double antibiotic paste (DAP) is obtained by mixing ciprofloxacin and metronidazole in equal proportions (1:1) (9).

In RCT, one of the biggest issues is the full eradication of intracanal medicaments that have stayed in root canals between treatment sessions (7). Prior research has revealed that it is impossible to completely flush or agitate away intracanal dressings from root canals (6,10). The influence of $Ca(OH)_2$ as an intracanal dressing on the accuracy of EALs has been explored in previous literature (5,6,11). Nevertheless, no research has assessed the impact of intracanal applications of DAP and TAP on the precision of EALs.

This study aimed to analyze the effect of various intracanal medicaments on the accuracy of four EALs. This study hypothesized that the accuracy of EALs would not vary significantly when exposed to various medication residues.

Materials and Methods

This laboratory study has been composed in accordance with the Preferred Reporting Items for Laboratory studies in Endodontology 2021 guidelines (12). The Erciyes University Clinical Research Ethics Committee gave their consent to conduct this study (decision no: 2020/110, date: 12.02.2020). The G*Power v.3.1.9.2 (Heinrich Heine, Düsseldorf University, Düsseldorf, Germany) program was employed to ascertain the necessary minimum sample size. An alpha-type error of 0.05, an effect size of 0.26 and a beta power of 0.80 were set, thus determining the minimal estimated sample size to be 160.

Selection and Preparation of Samples

This study used 160 extracted human maxillary central incisors. Radiographs were taken of the specimens in mesiodistal and buccolingual directions to verify the presence of straight single canals. Teeth with root canal obliteration, excessive coronal tissue loss, and internal or external resorption were excluded and replaced by two examiners (T.A., H.C.).

Testing was conducted after the teeth were submerged in a 0.1% thymol solution. Teeth were decoronated at the cementoenamel junction with a Minitome precision cutting device (Struers ApS, Ballerup, Denmark) to establish a fixed reference point. After locating the root canal orifices, canal patency was checked using a 10 K-type hand file (EndoArt, Incidental, İstanbul, Turkey). The root canals were enlarged using a 25 Wave One Gold rotary file system (Dentsply). During root canal preparation, the canals were irrigated with 2.5 mL of 2.5% NaOCl, followed by 2.5 mL of distilled water. Paper cones were utilized to dehydrate the canals, and appropriate root canal conditions were obtained prior to the application of intracanal medicaments.

Actual Working Length (AL) Determination

An experienced clinician (T.A.) ascertained actual working length using an operating microscope (OPMI Pico, Carl Zeiss Gmbh., Jena, Germany) at 10× magnification. A 25 K-type hand file was advanced until it could be seen apically. The rubber stopper of the file was fixed and a digital calliper was employed to measure the space between the file tip and the stopper. This measurement minus 0.5 mm yielded the actual working lengths.

Applying Medicaments to Canals

The samples were distributed into four groups (n=40) randomly with regard to the type of intracanal medication being used.

Group 1 [$Ca(OH)_2$]: $Ca(OH)_2$ powder (Kalsin; Spot Dis Deposu AS, İzmir, Turkey) and distilled water were mixed in a 1:1.5 proportion until a creamy consistency was obtained. The root canals were filled using a lentulo spiral until $Ca(OH)_2$ was visible at the apex.

Group 2 (DAP): DAP was obtained by mixing ciprofloxacin (Cipro, Biofarma, İstanbul, Turkey) and metronidazole (Nidazol, IE Ulagay, İstanbul, Turkey) in equal proportions (1:1). Sterile saline solution was used as a carrier to form a paste of the antibiotics and mixed until it reached a creamy consistency. The root canals were filled using a lentulo spiral until DAP was seen at the apex.

Group 3 (TAP): TAP was obtained by mixing ciprofloxacin, metronidazole, and minocycline (Skid, Zentiva, Frankfurt, Germany) in equal proportions (1:1:1). Sterile saline solution was used as a carrier to mix the antibiotic powder into a paste with a creamy consistency. The root canals were filled using a lentulo spiral until TAP was seen at the apex.

Group 4 (Control): In the control group, no intracanal medication was delivered into the root canals of the samples.

Detection of Electronic Lengths (EL)

The medicaments were left in the root canals of the samples for one week, and then the temporary fillings were removed.

No additional preparation was performed, and the root canals were irrigated with 17% EDTA using a 30-G needle. The specimens were embedded in a plastic mould filled with alginate, keeping 2 mm of the teeth crowns visible.

After randomly allocating 40 teeth to four subgroups (n=10), each subgroup was assigned an EAL measurement. Prior to measurement, the lip clip was placed in the alginate, and all measurements were completed within 2 hours to ensure that the alginate remained moist. A 25 K-type hand file (EndoArt, Incidental, İstanbul, Turkey) was used during the measurement.

All measurements were performed by an experienced clinician (H.C.) and conducted for each device following the instructions provided by the manufacturers. In these instructions, the markings on the products and how to interpret the numerical values were specified to indicate the apical constriction point.

Representative samples from each group were divided into two halves. Stereomicroscope images were then obtained to determine if the intracanal medicament in the root canals could be completely removed (Figure 1).

Statistical Analysis

All statistical analyses were carried out with SPSS 22.0 (SPSS Inc., IL, USA) employing an alpha value of 0.05. The normality of the data was examined with the Shapiro-Wilk test, which demonstrated that all data were normally distributed (p>0.05). The EL-AL scores for each medication group were categorized within the margin of ±0.5 and ± 1 mm, the chi-square (χ^2) test was utilized to contrast the precision of the EALs, with a significance level of 0.05.

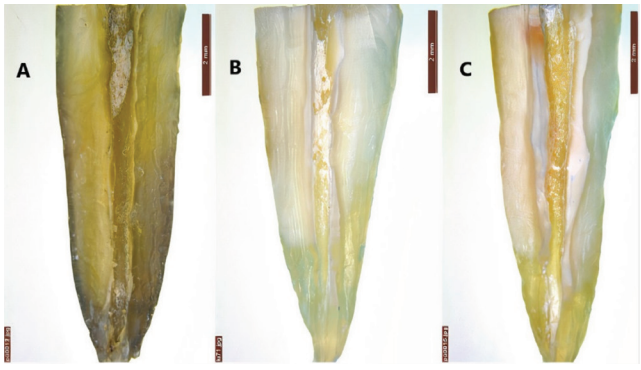

Figure 1. Representative stereomicroscope images of the root fragments (×10 magnification) showing the amount of residual medicament. (A) TAP, (B) DAP, (C) $Ca(OH_2)$

TAP: Triple antibiotic paste, DAP: Double antibiotic paste

Results

The descriptive statistics of EL-AL values of EALs tested in different medicament groups are presented in Table 1. No statistical variation was found between the four EALs when evaluating measurements in the presence of different intracanal medicaments, given the tolerance of ±0.5 and ±1 mm (χ^2 tests, p>0.05).

Figure 2 details the success levels of EALs based on intracanal medicaments staying within the ±0.5 mm tolerance limit.

In addition, no strong correlation was observed between the EL-AL differences and the type of residual medication [r=0.296 for $Ca(OH)_2$; r=0.025 for TAP; r=0.123 for DAP].

Discussion

No residual intracanal medication should be left in the root canals; otherwise, these residues could impede the successful integration of root canal filling materials with the root canal walls (13). Therefore, various irrigation agents and techniques have been proposed to take out intracanal dressings from the root canal. According to previous studies, $Ca(OH)_2$, DAP, and TAP could not be completely removed from the root canal (6,14,15). In contrast, EDTA showed significantly greater success in eliminating $Ca(OH)_2$ than other irrigation solutions (16,17). In addition, EDTA can be effectively used to remove antibiotic pastes from root canals (14,18). In light of these findings, 17% EDTA was utilized in this study to dislodge intracanal medicaments from the root canal.

The impact of using $Ca(OH)_2$ as an intracanal drug on the precision of apex locator devices has been investigated in previous studies with conflicting results (5,6,11). In the $Ca(OH)_2$ group in this study, there was no notable discrepancy in the measurement accuracies of the four EALs at the ±0.5 and ±1 mm tolerance limits (p>0.05). Our results are consistent with those of Shojaee et al.'s (11).

Table 1. Mean and standard deviation of EL-AL values of four EALs in the presence of different medicaments

	Raypex 6 (mean ± SD) (mm)	Ipex 2 (mean ± SD) (mm)	Apex ID (mean ± SD) (mm)	Propex Pixi (mean ± SD) (mm)
$Ca(OH)_2$	0.151±0.167	0.0450±0.134	-0.260±0.337	-0.276±0.187
TAP	0.120±0.120	-0.0630±0.250	-0.0130±0.283	-0.192±0.204
DAP	-0.0280±0.174	-0.182±0.223	0.0660±0.284	-0.167±0.190
Control	0.178±0.129	-0.038±0.132	-0.089±0.304	-0.19±0.148

Negative values as the mean indicate shorter measurements than the actual length, while positive means indicate longer measurements than the actual length. EAL: Lectronic apex locators, SD: Standard deviation, TAP: Triple antibiotic paste, DAP: Double antibiotic paste

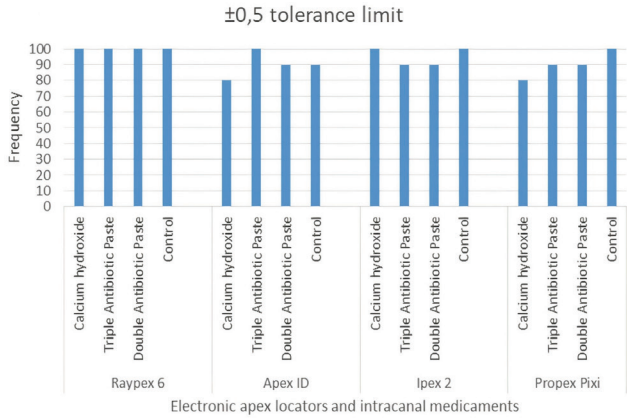

Figure 2. The percentage of measurement accuracy of EALs in the presence of intracanal medicaments within the tolerance limit of ±0.5 mm

EAL: Lectronic apex locators

This might be because the EALs used in both studies operated at nearly equal frequencies. Although there was no discernible statistical variation in the accuracy of EALs, Raypex 6 and Ipex 2 showed more consistent results than other EALs used in the $Ca(OH)_2$ group within the tolerance limit of ±0.5 mm. This might be due to variations in the apical anatomy of samples.

Analyses did not reveal any noteworthy variation in the precision of the four EALs when taking into account the ±0.5 and ±1 mm boundary conditions in the DAP and TAP groups ($p>0.05$). Considering the composition of DAP and TAP, only TAP contains minocycline. Minocycline is an antibiotic containing tetracycline, and it has a slight effect on removing the smear layer (19). Due to potential surface modifications caused by the smear layer's removal, such as the opening of tubules on the root dentin surface, dissolution of the inorganic structure, and movement of the dentin fluid (20) electronic measurement results may be affected. However, the lack of differences in the statistical results indicate that the antibiotic with the active ingredient minocycline did not significantly affect modern EALs. This might be because minocycline is a weak chelating agent at low doses and induces limited demineralization on the dentin surface (21).

Although no noteworthy distinction was observed between Raypex 6 and Apex ID in the TAP group, Raypex showed a higher accuracy in the DAP group, compared with other EALs, within the tolerance limit of ±0.5 mm. Due to the similar frequency ranges of EALs used in this study, no statistically significant difference may have occurred; however, small variations in frequencies may lead to small differences in the percentage of accuracy.

$Ca(OH)_2$, DAP and TAP groups showed less consistent results than the control group in measurements made with Propex Pixi. In the measurements made with Apex ID, the most consistent results were obtained in the TAP group, while the most inconsistent results were obtained from the $Ca(OH)_2$ group. However, these results as percentages are not statistically significant ($p>0.05$). These results may be due to the differences of apical anatomy in the samples.

The strengths of the present study are that the electronic measurement with EALs performed by another clinician who is unaware of the actual length measurements carried out under the operating microscope, and the differences between ELs and ALs were evaluated at a precision of 0.01 mm. All the EALs in this research showed optimum results with 100% accuracy in the four groups within the tolerance limit of ±1 mm. This was consistent with the findings of other studies in the literature (22). It is thought that the reason for the high accuracy rate within the 1 mm error range of the EALs tested in this study could be attributed to the remarkable technical characteristics of these contemporary EALs.

One of the shortcomings of this study was its *in vitro* nature hence the results of this study need to be verified *in vivo*. More research in a laboratory setting and in clinical trials is needed to back up the discoveries of this study.

Conclusion

Within the confines of this study, contemporary EALs equipped with advanced technology were dependable in setting the working length despite the presence of DAP, TAP, and $Ca(OH)_2$ residue in the root canal.

Ethics

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee gave their consent to conduct this study (decision no: 2020/110, date: 12.02.2020).

Informed Consent: This study does not require informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.C., Concept: H.C., T.A., B.K., Design: H.C., T.A., Data Collection or Processing: H.C., T.A., Analysis or Interpretation: T.A., Literature Search: H.C., T.A., B.K., Writing: H.C., B.K.

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Original Article / Özgün Araştırma

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The Genotype-phenotype Correlation of HLA-DQ2 and HLA-DQ8 Haplotypes in Pediatric Celiac Disease: A Single Center Experience

Çocuk Çölyak Hastalarında HLA-DQ2 ve HLA-DQ8 Haplotiplerinin Genetik ve Fenotip ile Korelasyonu: Tek Merkez Deneyimi

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Abstract

Objective: Celiac disease (CD) is a multifactorial disease caused by the interaction of HLA-DQA1 and HLA-DQB1 alleles, which are known to be associated with disease susceptibility in addition to gliadin and other environmental factors. The aim of this study was to determine the incidence of genetic alleles in pediatric CD at our center.

Materials and Methods: This study was designed as a retrospective evaluation of the clinical and genetic findings of patients followed up with a diagnosis of CD in the Pediatric Gastroenterology Outpatient Clinic. According to the study; the data of age, compliance with the diet, family history of disease, genetic testing outcomes, and Marsh classification were compared.

Results: A total of 138 CD patients (94 female, 44 male) were included in our study. The most frequent genetic allele was HLA-DQ2 (69.6%). There was no significant relationship between genetic results and gender, age at diagnosis, body mass index, monthly growth rate, and compliance with diet. In addition, no relationship was found between the genetic structure of the patients and their positive family history with CD. In our study, type 1 diabetes mellitus (DM) was the most frequent disease accompanying CD. Remarkably, higher concomitant positivity of DQ2(+) and DQ8(+) was found in patients presenting with CD and type 1 DM co-existence.

Conclusion: Genetic tests are used for the exclusion of CD disease, rather than diagnosis of. The importance of genetic testing to reduce interventional procedures for CD must be acknowledged.

Keywords: Pediatric, celiac disease, genetic mutations, HLA-DQ2, HLA-DQ8

Öz

Amaç: Çölyak hastalığı (ÇH), gliadin ve diğer çevresel faktörlere ek olarak hastalık duyarlılığı ile ilişkili olduğu bilinen HLA-DQA1 ve HLA-DQB1 alellerinin etkileşimi ile ortaya çıkan multifaktöriyel bir hastalıktır. Bu çalışmanın amacı, merkezimizde pediatrik ÇH'de genetik allel insidansını ortaya koymaktır.

Gereç ve Yöntemler: Bu çalışma Pediatrik Gastroenteroloji Polikliniği'nde ÇH tanısı ile takip edilen hastaların dosyalarının değerlendirilmesi şeklinde retrospektif olarak tasarlanmıştır. Hastaların yaş, diyet uyumları, ailede hastalık hikayesi, genetik testleri ve Marsh sınıflamaları istatistiksel olarak karşılaştırılmıştır.

Bulgular: Çalışmaya toplam 138 ÇH tanılı çocuk (94 kız, 44 erkek) dahil edilmiştir. HLA-DQ2 haplotipi hastalarda en sık (%69,9) saptadığımız genetik alleldir. Saptadığımız genetik haplotip ile hastaların cinsiyet, tanı yaşı, vücut kitle indeksi, aylık büyüme oranları ve diyet uyumu arasında anlamlı bir ilişki bulunamamıştır. Aile öyküsünde ÇH varlığı ile genetik mutasyon arasında da bir ilişki

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bulunamamıştır. Çalışmamızda, ÇH'ye en sık tip 1 diabetes mellitus (DM) varlığının eşlik ettiği saptandı. HLA DQ2 ve HLA DQ8 allellerinin birlikte pozitifliği, özellikle ÇH ve tip 1 DM hastalığı birlikte olan çocuklarda belirgin olarak yüksek saptanmıştır.

Sonuç: Genetik testler, ÇH tanısından ziyade hastalığın dışlanması için kullanılır. Genetik testlerin yapılması, gereksiz yere yapılan girişimsel işlemleri azaltmak açısından önemlidir.

Anahtar Kelimeler: Çocuk, çölyak hastalığı, genetik mutasyonlar, HLA-DQ2, HLA-DQ8

Introduction

Celiac disease (CD) is a systemic autoimmune disease that may be presented with gastrointestinal findings causes malabsorption. A wide variety of non-gastrointestinal findings are also seen in most of the patients (1). Its frequency is thought to be around 1% while differences may be seen between countries depending on socioeconomic, cultural, and environmental factors (2). CD is a multifactorial disease that occurs with the interaction of HLA-DQA1 and HLA-DQB1 allelic variants, which are known to be associated with disease susceptibility, and lesser known non-HLA genes, gliadin and other environmental factors (3). HLA-DQ2 and HLA-DQ8 haplotypes, determined by molecular genetic analysis of HLA-DQA1 and HLA-DQB1 allelic variants, are the most important genetic risk factors associated with susceptibility to CD (4). HLA-DQ2 and HLA-DQ8 haplotypes are transcribed from major histocompatibility complex class II genes, localized on chromosome 6. DQ2 and DQ8 α/β heterodimers mediate the activation of gluten-reactive CD4 T cells in the gut. As a result of this, a T-cell response occurs and produce disease specific antibodies, resulting to secretion of pro-inflammatory cytokines that may cause the mucosal atrophy and clinical findings (5). The prevalence of these haplotypes in the general population is about 30-40%, whereas only approximately 1% of the population have CD. So, this means genetic haplotype positivity is necessary, but not sufficient, to cause CD (6-8). While the presence of HLA structure and gluten contact is strictly required, it is not sufficient in the development of CD (9).

Material and Methods

This study was designed as a retrospective evaluation of the clinical and genetic findings of the patients followed up with the diagnosis of CD between 1-18 years of age in the Pediatric Gastroenterology Outpatient Clinic in University of Health Sciences Turkey, Adana City Training and Research Hospital between 15.10.2017-01.11.2020. Ethics approval was obtained from Adana City Training and Research Hospital Ethics Committee (decision number: 1123, date: 04.11.2020).

According to the study; the age of diagnosis, growth rate calculations in the follow up visits (3, 6, and 12 months), presence of presenting symptoms, compliance with the diet, family history of disease, and genetic testing outcomes were compared with Marsh classification. The growth rate measurements of the patients was calculated using https://cedd.saglik-network.org software program. We aimed to analysed the genetic HLA-DQ2 and HLA-DQ8 gene positivity rates and allele distribution in CD and the relationship with different parameters of the patients.

DNA Extraction and Genetic Analysis

Patients' genomic DNA was extracted from peripheral blood sample using QIAGEN QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to the protocol of the isolation kit. The Qubit® 3.0 Fluorometer (Thermo Fisher Scientific, US) was used to verified DNA integrity. Analysis of HLA-DQA1 and HLA-DQB1 alleles were performed with Genvinset® HLA Celiac Real-Time PCR Assay. According to this, samples which had both DQA1*05 and DQB1*02 alleles were considered as DQ2 positive. If there is only DQA1*05 or DQB1*02 allele, these samples had named half DQ2 positive. Samples which had both the DQA1*03 and DQB1*03:02 alleles, they were considered as DQ8 positive.

Statistical Analysis

All the statistical analyses were carried out using IBM SPSS Statistics Version 20.0 statistical software package. Numbers and percentages were used to express categorical variables. At the same time continuous variables were expressed as mean and standard. Fisher's exact test was used to compare categorical variables between the genetic groups. The Shapiro-Wilk test was carried out to confirm the normality of distribution of continuous variables. One-way ANOVA was used to compare genetic groups. To appraise the change of the growth rate in time, the Repeated Measurements Analysis was applied. While evaluating the results, values less than 0.05 were considered statistically significant.

Results

A total of 138 patients with diagnosis of CD were included in the study. Ninety-four of the patients were female and 44 were male. All of subjects enrolled in the study had received the diagnosis of CD according to the the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition 2012 guideline through the pathologic examination of gastroscopic biopsy performed based on clinical findings or laboratory test positivity (10). Patients' demographic characteristics are summarized in Table 1. HLA DQ2 genetic was the most frequent genetic positivity (69.6%) in patients diagnosed with CD. HLA DQ8 genetic positivity was seen in 11 patients diagnosed with CD (8%). HLA DQ2 and HLA DQ8 genetic tests were negative in 4 patients. The distribution of HLA genetic of the patients was shown in Table 2. No significant relationship was found when genetic

Table 1. General features of the subjects	
Gender, n (%)	
Male	44 (32%)
Female	94 (68%)
Age (years), mean ± SD	12.3±4.0
Min-max	4.3-20.8
Age of diagnosis (years), mean ± SD	7.5±4.1
Min-max	0.8-17.7
Compliance to diet n (%)	103 (75%)
Presence of admission complaint n (%)	118 (86%)
Those with a family history = 2 n (%)	72 (52%)
Concomitant disease n (%)	
None	108 (78%)
Type 1 diabetes	14 (10%)
Thyroiditis	3 (2%)
Cystic fibrosis	3 (2%)
Down syndrome	2 (2%)
Other	8 (6%)
3-month growth rate, mean ± SD	1.54±0.66
6-month growth rate, mean ± SD	3.04±1.37
12-month growth rate, mean ± SD	6.20±2.65
BMI, mean ± SD	17.6±3.8
Marsh (Histopathological analysis)	
1	2 (1%)
2	1 (1%)
3a	46 (34%)
3b	58 (43%)
3c	28 (21%)
SD: Standard deviation, BMI: Body mass index	

Table 2. The distribution of subjects according to HLA-DQ2 and HLA-DQ8 genetic positivity		
Genetic	**Number**	**Percentage (%)**
DQ2 (+)	96	69.6
DQ2 (+) DQ8 (+)	10	7.2
DQ8 (+)	11	8.0
Half DQ2 (+)	7	5.1
Half DQ2 (+) DQ8 (+)	10	7.2
Normal	4	2.9

features were compared to gender, age of diagnosis, body mass index (BMI), monthly growth rate, and compliance to diet. No correlation was found between genetic features and the patients complaints on admission. No relationship was found between the genetic distribution of the patient and the presence of CD in the family. Table 3 summarizes the comparison of some parameters with the genetic distribution. Type 1 diabetes mellitus (DM) is the most frequent disease accompanying with CD. According to our results, the attendant positivity of HLA-DQ2 and HLA-DQ8 alleles together are significantly higher in patients with CD and type-1 DM co-existence. But this is not statistically significant due to the limited number of patients. A review of genetic features at the allele level is summarized in Table 4. No correlation was found between alleles in patients with respect to the age of diagnosis, gender, monthly growth rates, BMI, compliance to diet, presence of complaints at admission, family history, and Marsh classification. However, the rates of complaints at admission in patients with A1*03 - B1*03:02 combination (DQ2) (64%) and in those with A1*05 - B1*02 - A1*03 - B1*03:02 combination (DQ2 and DQ8 together) (67%) were much lower compared to the other groups despite not being statistically significant. Assessment of the patients for presence of concomitant diseases between alleles showed that type 1 DM was higher in patients with A1*05 - B1*02 - A1*03 - B1*0302 combination (DQ2 and DQ8 together) compared to others. However, due to the small number of patients, it was not considered statistically significant. Therefore, further studies according larger number of patients are required.

Although an increase was observed ($p<0.001$) over time in growth rates at 3, 6, and 12 months for all groups as evaluated during outpatient follow-up, this difference was not associated with the alleles carried ($p=0.101$). A more detailed evaluation of the results actually suggests that it may be a distinctive feature for this allele based on the fact that the growth rate at 3 months is the lowest with the A1*05 allele and the growth rate was still low at 12 months. This conclusion cannot be extrapolated while only 4 patients are found here, and studies are needed with a larger number of patients (Figure 1). No significant association was found between the genetic structures and the growth rates of the patients. The annual growth rate was higher in patients (4 patients) with negative HLA-DQ2 and DQ8 (Figure 2).

Discussion

The most frequent genetic structure in CD was complete positivity of HLA DQ2 (69.6%) and it is similar to the literature followed by HLA DQ8 genetics (8%). In the literature the most frequent allele in CD was HLA-DQ2 (90%) (3). In the subject group in this study, however, genetic distributions were different from the literature. The genetic distribution may vary according to the regional and ethnic aspects of the country. A different study that was conducted in our region (11) showed that the rates of HLA-DQ2 with HLA-DQ8 positivity, HLA-DQ2 positivity, and HLA-DQ8 positivity were

76%, 67% and 25%, respectively. The proportion of patients with HLA-DQ2 positivity in our study (69.6%) was similar to the proportion of patients with HLA-DQ2 positivity in that study (67%). The proportion of HLA-DQ8 positivity (8%), however, was different from the proportion of patients in the same study with HLA-DQ8 positivity (25%). There are also studies in the literature where HLA-DQ8 positivity in CD is consistent with our study (2% in Italy, 2.3% in Hungary, and 6.4% in Finland) (12). HLA-DQ2 and HLA-DQ8 genetic tests were negative in 2.9% of the subjects. Consistent with the rates given in the literature, the rates of negativity with HLA-DQ2 and HLA-DQ8 in CD were 0% and 10% (13). Some studies in the literature are supportive of our result; patients with CD are found to be negative for DQ2 and DQ8 at a rate of 3.4% (1). Although DQ variants are not sufficient for the development of the disease. The negative predictive value

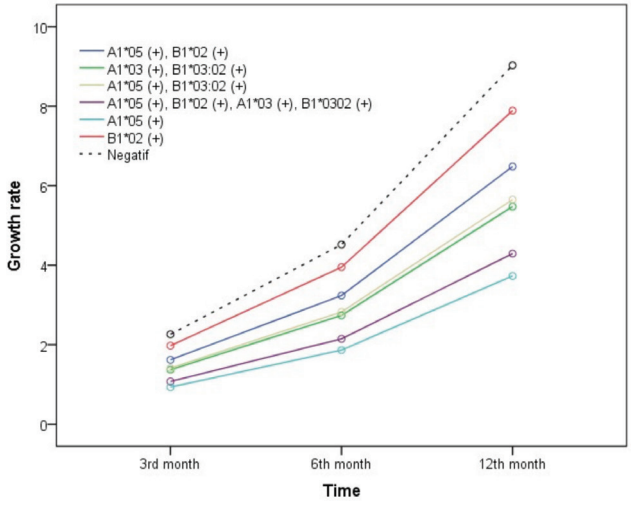

Figure 1. Growth rates comparison of the patients based on the HLA genetic allele structure

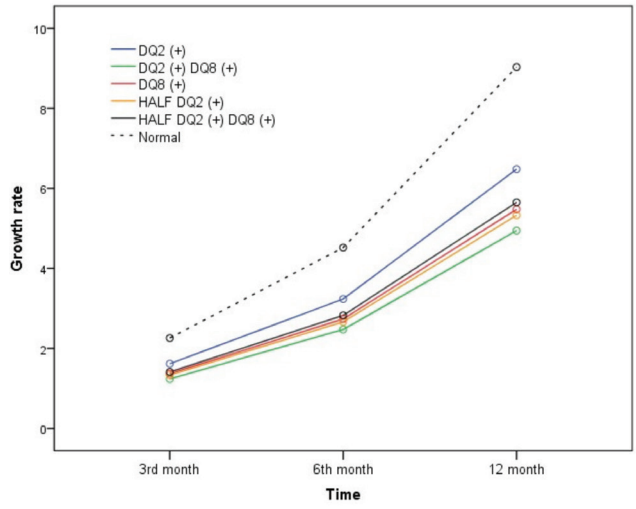

Figure 2. Comparison of growth rates in patients based on the HLA-DQ2 and DQ8 characteristics

Table 3. Genetic features compared with some parameters of the patients

	DQ2 (+)	DQ2 (+) DQ8 (+)	DQ8 (+)	HALF-DQ2 (+)	HALF-DQ2 (+) DQ8 (+)	Normal	p-value
n	96	10	11	7	10	4	
Age	12.5±4	12.1±3.9	12±3.7	12.6±4.5	11.2±4	11.1±5.7	0.930
Age of diagnosis	7.7±4.1	7.8±4.5	6.4±3.3	7.4±4.6	6.4±4	7.3±5.5	0.868
12-month growth rate	6.48±2.7	4.94±2.8	5.48±1.26	5.33±2.93	5.65±2.47	9.0±0	0.345
BMI	17.8±3.8	16.3±2.3	17.5±3.6	19.6±6.8	16.4±2.6	17.8±5.2	0.687
Compliance to diet	73 (76%)	5 (50%)	9 (82%)	6 (86%)	7 (70%)	3 (75%)	0.533
Female gender	67 (70%)	6 (60%)	7 (64%)	6 (86%)	6 (60%)	2 (50%)	0.758
Presentation	84 (88%)	7 (70%)	7 (64%)	7 (100%)	9 (90%)	4 (100%)	0.146
Those with a family history = 2	52 (54%)	6 (60%)	3 (%27)	4 (57%)	6 (60%)	1 (25%)	0.108
Concomitant disease							
None	80 (83%)	4 (40%)	8 (73%)	5 (71%)	9 (90%)	2 (50%)	0.005
DM	7 (7%)	6 (60%	1 (9%)	0 (0%)	0 (0%)	0 (0%)	
Thyroiditis	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
CF	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	
Down	1 (1%)	0 (0%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	
Other	3 (3%)	0 (0%)	1 (9%)	2 (29%)	1 (10%)	1 (25%)	

n: Number, BMI: Body mass index, DM: Diabetes mellitus, CF: Cystic fibrosis

Table 4. Distribution of genetic alleles in patients and associated parameters								
	A1*05 (+), B1*02 (+)	A1*03 (+), B1*03:02 (+)	A1*05 (+), B1*03:02 (+)	A1*05 (+), B1*02 (+), A1*03 (+), B1*03:02 (+)	A1*05 (+)	B1*02 (+)	All Negative	p-value
n	95	11	10	9	4	2	4	
Presence of complaints at admission	83 (87%)	7 (64%)	9 (90%)	6 (67%)	4 (100%)	2 (100%)	4 (100%)	0.219
Concomitant disease								
None	79 (83%)	8 (73%)	9 (90%)	4 (44%)	2 50%	2 (100%)	2 (50%)	0.015*
DM	7 (7%)	1 (9%)	0 (0%)	5 (56%)	0 (0%)	0 (0%)	0 (0%)	
Thyroiditis	3 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
CF	2 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (25%)	
Down	1 (1%)	1 (9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Other	3 (3%)	1 (9%)	1 (10%)	0 (0%)	2 (50%)	0 (0%)	1 (25%)	

n: Number, BMI: Body mass index, DM: Diabetes mellitus, CF: Cystic fibrosis

of not harboring DQ gene is considered to be 100% (14). Routine use is not recommended since genetic analyses are costly and difficult to work with and unable to establish the diagnosis. Megiorni et al. (15) found in their study associating HLA groups with gender, that DQ2 and/or DQ8 carrying was higher in females and DQ2/DQ8 negativity was more frequent in males. In our study, no relationship was found between the genetic features of the patients and gender. As stated in the literature, the HLA-DQ2 haplotype positivity was associated with early onset disease, while the presence of the HLA-DQ8 haplotype was associated with adult-onset disease rather than child-onset (16). However, the association between the age of diagnosis and genetic features was not statistically significant in our study (p=0.868). No significant relationship was found between the body mass index, monthly growth rate and compliance to diet. Some studies (3,5) have shown that there is a positive relationship between the DQ2 allele and mucosal damage. However, no relationship was found between the patient's genetic structure and Marsh classification and the presence of CD in the family. Despite being conducted with a small number of patients (17,18) some studies did not find a significant relationship between carrying HLA-DQ2 and DQ8 and the age of diagnosis or the clinical presentation. Although the complaints were shown to be lower in patients with negative HLA-DQ2 and HLA-DQ8, no relationship was found in our study for the presence of complaints at admission or diagnosis by chance in terms of genetic features (11).

Type 1 DM is the most frequent disease accompanying with CD. In particular higher concomitant positivity of DQ2 (+) DQ8 (+) in patients presenting with CD and type 1 DM co-existence is remarkable despite not being statistically significant due to the limited number of patients.

No correlation was found between alleles in patients with respect to the age of diagnosis, gender, monthly growth rates, BMI, compliance to diet, presence of complaints at admission, family history, and Marsh classification. However, the rates of complaints at admission in patients with A1*03-B1*03:02 combination (DQ2) (64%) and in those with A1*05, B1*02, A1*03, B1*0302 combination (DQ2 and DQ8 together) (67%) were much lower compared to the other groups. Assessment of the patients for presence of concomitant diseases between alleles showed that type 1 DM was higher in patients with A1*05 - B1*02 - A1*03 - B1*0302 combination (DQ2 and DQ8 together) compared to others. However, this was not statistically significant due to the small number of patients. However, further studies with a larger number of patients are required. Although an increase was observed ($p<0.001$) over time in growth rate at 3, 6, and 12 months for all groups as evaluated during outpatient follow-up, this difference was not associated with the alleles carried (p=0.101). A more detailed evaluation of the results actually suggests that it may be a distinctive feature for this allele based on the fact that the growth rate at 3 months is the lowest with the A1*05 allele and the growth rate was still low at 12 months. This conclusion cannot be extrapolated while only 4 patients are found here, and studies are needed with a larger number of patients. The limitations of our study is the number of the patients.

Conclusion

In the guidelines that are updated in time through cumulative knowledge and experience, HLA genetic studies were included in the diagnostic algorithm in some cases to support the diagnosis of CD. Genetic tests are used for exclusion of CD disease, rather than diagnosis of. The presence of HLA-DQ2 or HLA-DQ8 has a negative predictive value of

near 100% and may be used to exclude the diagnosis of CD but it is still not sufficient for diagnosis. The importance of genetic testing to reduce interventional procedures for CD must be acknowledged.

Ethics

Ethics Committee Approval: Ethics approval was obtained from University of Health Sciences Turkey, Adana City Training and Research Hospital Ethics Committee (decision number: 1123, date: 04.11.2020).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: D.G.T., Ö.A., Concept: D.G.T., Design: D.G.T., Ö.A., Data Collection or Processing: D.G.T., Ö.A., Analysis or Interpretation: Ö.A., Literature Search: D.G.T., Ö.A., Writing: D.G.T., Ö.A.

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Side Effects of Radiation Therapy in Patients with Head and Neck Cancer According to the Late Effects of Normal Tissues-Subjective Objective Management and Analytic Questionnaire

Late Effects of Normal Tissues-Subjective Objective Management and Analytics Anketine Göre Baş Boyun Kanserli Hastalarda Radyasyon Tedavisinin Yan Etkileri

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Abstract

Objective: The present study explored the oral side effects of radiation in patients with head and neck malignancies.

Materials and Methods: The study sample consisted of 60 patients who were candidates for radiation therapy and had head and neck malignancies. After collecting each patient's demographic information, the late effects of normal tissue-subjective objective management and analytic questionnaire were used to verify the diagnostic and treatment data.

Results: Sore throat, otalgia, and pain in the jaw and mouth were the most common complaints among patients receiving therapy, whereas toothache was the least common. After one and three months of therapy, 60% and 80% of the patients, respectively, exhibited severe xerostomia. Before beginning therapy, 73.3% of patients did not have any difficulty chewing.

Conclusion: Following one month of therapy, these adverse effects reach their maximum rate, and from then until the end of the third month after treatment, they continue to improve until they are near to their pre-treatment levels.

Keywords: Radiotherapy, head, neck, cancers

Öz

Amaç: Bu çalışma, baş ve boyun maligniteleri olan hastalarda radyasyonun oral yan etkilerini araştırmaktadır.

Gereç ve Yöntemler: Çalışmanın örneklemini radyasyon tedavisine aday olan ve baş-boyun malignitesi olan 60 hasta oluşturmuştur. Her hastanın demografik bilgileri toplandıktan sonra, teşhis ve tedavi verilerini doğrulamak için normal doku-öznel objektif yönetimin ve analitik anketin geç etkileri kullanıldı.

Bulgular: Boğaz ağrısı, otalji, çene ve ağızda ağrı tedavi alan hastalarda en sık görülen şikayetler iken diş ağrısı en az görülen şikayetlerdi. Bir ve üç aylık tedaviden sonra hastaların sırasıyla %60 ve %80'inde ciddi ağız kuruluğu görüldü. Tedaviye başlamadan önce hastaların %73,3'ünde çiğneme güçlüğü yoktu.

Sonuç: Bir aylık tedaviden sonra bu yan etkiler maksimum oranlarına ulaşır ve tedaviden sonraki üçüncü ayın sonuna kadar tedavi öncesi seviyelerine yaklaşana kadar düzelmeye devam eder.

Anahtar Kelimeler: Radyoterapi, baş, boyun, kanserler

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Introduction

The global incidence of oral cavity, pharynx, and larynx cancer is around 500,000 cases yearly, with an average yearly mortality rate of 270,000. Head and neck cancer accounts for approximately 4% of these malignancies (1). Except for skin cancer, these instances represent 5% of all cancer-related mortality, with about three-quarters attributable to oral cavity and pharynx malignancies and the remaining 1.4% attributable to laryngeal cancer (2).

Radiotherapy is one of the primary treatments that is sometimes used alone and sometimes in conjunction with other treatments (3). In situations of irradiation of the oral cavity and salivary glands, problems such as the death of taste bud cells, the diminution of salivary gland secretory function, oral mucositis, and peripheral neuropathy are unavoidable. These patients frequently feel dry mouth, altered taste perception, difficulty in opening the mouth (trismus), and difficulty in swallowing (dysphagia) (4).

Another problem is radiation-induced somatic nerve damage, which produces discomfort. 30-80% of patients with cancer endured discomfort. Pain in the oropharynx, face, or neck, or as a headache, is the initial clinical finding in these individuals (5).

The limited studies have been conducted based on patients' complaints about the oral side effects of radiotherapy, and have only addressed a few oral side effects, and no study using this questionnaire has been conducted on the Iranian population. Therefore, the purpose of this study is to investigate the side effects of radiation therapy in patients with head and neck cancer according to the late effects of normal tissues - subjective objective management and analytic (LENT-SOMA) questionnaire.

Material and Methods

This work is descriptive-analytical research about 60 patients with head and neck malignancies referred to "Shafa Hospital" in Kerman before, during, and one to three months following radiation between 2018 and 2019.

The inclusion criteria of the present study was the presence of primary cancer in the head and neck region requiring radiation as primary or adjunctive therapy. The patient must be free of oral mucosa disorders and systemic conditions impacting saliva. Exclusion criteria include cancer recurrence in the investigated regions and individuals who have had a significant resection.

The LENT-SOMA questionnaire, which is regarded as a valid questionnaire in the field of oral diseases, has been utilized after recording the demographic information of each patient through interview and file review to verify diagnostic and treatment information (6,7).

The validity and reliability of the applied questionnaire has been established by Rabiei et al. (8). The final year student performed the Persian version of the LENT-SOMA questionnaire as a control for all patients prior to radiation treatment, during radiotherapy treatment (7 to 14 days from the start of radiotherapy) and one to three months after the conclusion of radiotherapy treatment. The goal of the study was first explained to each participant, and they were provided with the questionnaire if desired. In addition, all respondents were promised that the information they provided on the questionnaire would remain secret and would be studied solely from a statistical standpoint; the questionnaire was also anonymous (verbal consent). This project was approved by the Ethical Committee of Kerman University of Medical Sciences of the university with the code IR.KMU.REC.1399.488 (date: 17.08.2023).

Statistical Analysis

The data analysis was performed using chi-square, ANOVA, and SPSS 21 (IBM SPSS Statistics V21, SPSS Inc., Chicago, Ill., USA).

Results

This research investigated sixty patients. Thirty patients completed the questionnaire before and during therapy, and rest of them completed the questionnaire before, during, and one and three months following treatment. The age ranges of the patients was 81 to 25 years, with an average age of 59.49.3 years (Table 1).

The minimum and maximum radiation dosages were 700 and 6,900 cGy, respectively. The most prevalent site of involvement was the larynx in 14 individuals (23.3%), followed by the nasopharynx in 9 people (15%), the hypopharynx in 6 people (10%), the tonsil in 4 people (6.7%), the oropharynx in 6 people (10%), and the oropharynx in 7 people (11.7%) (Table 2).

Before beginning radiation therapy, all patients described their discomfort as bearable. Most locations had a more severe kinds of pain during and one month after treatment. One month following treatment, the most extreme pain or type of sciatica was reported in the majority of affected locations.

One month following therapy, mouth discomfort (16.6%), ear ache (63.3%), jaw pain (6.6%), and sore throat (6.6%) were regarded as excruciatingly painful. After three months of therapy, pain severity decreased in all locations (Table 2).

Table 1. The demographic characteristics of study participants

Variable		No	%
Gender	Male	25	41.6
	Female	35	58.4
Profession	Employed	41	68.3
	Non-working	19	31.7
Education	Diploma≥	31	51.6
	>Diploma	29	48.4

50% of ear discomfort, 53.3% of throat pain, 40% of jaw pain, and 16.6% of mouth pain were unbearably unpleasant throughout therapy. Three months following radiation, 98 % of patients reported frequent discomfort and four patients reported terrible pain in these locations (Table 3).

A month after radiation therapy, 89% of patients with a sore throat, 81.2% of patients with mouth pain, 82.5% of patients with ear discomfort, 79.2% with jaw pain, and 61.3% of patients with tooth pain utilized housing constantly.

By separating the analyzed periods within one month following treatment, the severity of discomfort, the frequency of pain complaints, and the frequency of taking medication to ease pain in the throat, ear, jaw, and mouth were considerably higher than at other times (p=0.001). Additionally, the degree of toothache was greater one month after therapy than on other occasions.

After one and three months of therapy, 60% and 80% of patients, respectively, exhibited significant xerostomia.

Before beginning therapy, 73.3% of patients had no difficulty chewing. The data analysis about patients conducted over the course of one month revealed that 36.6% had trouble chewing hard foods, and 16.6% had difficulty eating soft foods. 98% of patients could not swallow soft meals one month following therapy, while 93,4 % were unable to consume beverages at this time. However, three months following therapy, a more significant proportion of patients were able to chew soft meals with more ease (Table 4).

This study revealed that, after adjusting for age and gender, changes in the sensation of taste, dysphagia, the frequency of experiencing dry mouth, the severity of xerostomia, and its influence on chewing different types of food were substantially greater one month after therapy than at previous periods (p=0.001).

One month after radiotherapy, the consequences of irradiation were identified in some variables. The pain in the ear and jaw exhibited a statistically significant association with the radiation dosage (p=0.001). Also, the present findings showed an increase in the rate of discomfort with age and gender (p=0.001).

Discussion

This study investigated the oral side effects of radiation in patients before, during, and one month and three months following treatment according to the LENT-SOMA questionnaire.

Compared to the research work by Rabiei et al. (8), the present study reveals that 60% of patients comprehend their pain experience since initiating therapy. In other investigations, pain has been identified as the most common side effect of radiation, with incidence rates ranging from 30% to 80% (9). Oral mucositis pain is the most prevalent symptom affecting mouth and jaw function (10).

In the study conducted by Elting et al. (11), the severity of mucositis and associated discomfort lessened throughout the sixth month (12).

The majority of patients related their pain to the tumor and/or cancer treatment. Whereas 59% reported their pain to be less severe than they expected, 29% were not satisfied with their level of pain despite pain management during cancer therapy. The most common neuropathic pain descriptors chosen were aching (20%) and burning (27%); nociceptive words chosen were dull (22%), sore (32%), tender (35%), and throbbing (23%), and affective/evaluative descriptors were tiring (25%) and annoying (41%).

Rose-Ped et al. (13) showed that painful sore throat takes place the most frequently (20%), followed by mouth sores and pain (18%), and dry mouth (14%) (13%).

One and three months following therapy, 60% and 80% of patients, respectively, exhibited significant xerostomia, which is less than the finding by Rabiei et al. (8).

Dirix et al. (14) research showed that dry mouth improved three to four weeks following radiation.

Three months following therapy, the process of restoring the sense of taste is nearing completion. Consistent with the observations of Yamashita et al. (15), Rabiei et al. (8), and Chen et al. (16). In the research by Shenoy et al. (7), some improvement of the sensation of taste occurred between 20

Table 2. The Otalgia, toothache, jaw pain, mouth pain, sore throat in patients

Pain	No of patients: 30				*p-value	No of patients: 30								**p-value
	Before therapy		During therapy			Before therapy		During therapy		One month after therapy		Three months after therapy		
	n	%	n	%		n	%	n	%	n	%	n	%	
Otalgia	0	0	5	16.6	0.01£	0	0	6	20	7	23.3	2	6.6	0.001£
Toothache	0	0	0	0	0.21	0	0	0	0	2	6.6	1	3.3	0.05
Jaw pain	1	3.3	2	6.6	0.08	2	6.6	3	10	5	16.6	1	3.3	0.04£
Mouth pain	1	3.3	2	6.6	0.08	1	3.3	2	6.6	5	16.6	0	0	0.05
Sore throat	3	10	9	30	0.01£	1	3.3	12	40	10	33.3	2	6.6	0.001£

*Chi-square, **ANOVA, £ P<0.05

and 60 days following the conclusion of therapy, and it was totally restored four months later.

Trismus is common following radiation. In the research by Rabiei et al. (8), 9.8% of patients had trismus of the head and neck muscles, which persisted after three months of therapy. In McSweeney's (17) study, there was no significant change in the mouth opening rate during the first 1-9 months after radiation treatment.

Ozdere et al. (18) showed that trismus is a commonly observed sequela in patients who have undergone radiation therapy to treat malignancies of the head and neck.

According to the present findings, the adverse effects of radiotherapy were a pain in the ear and jaw region and exhibited a statistically significant association with the radiation dosage one month after treatment, and discomfort in the mouth region increased with age and gender.

Patients who undergo RT for HNC can develop hearing especially when receiving 60 Gy. Complaints include ear heaviness, earache, decreased hearing, tinnitus, and dizziness (19).

Epstein et al. (12) showed that as radiation exposure rose, somatic nerve injury increased, followed by pain in the regions exposed to radiation. In the research by Rabiei et al. (8), increasing the dosage was associated with ear and tooth discomfort.

Around 1950, external beam radiotherapy was performed with a device that produced a voltage greater than 300 kvp. After that, with the development of cobalt devices in the 1950s and 1960s, kilovoltage devices were used less. It is worth mentioning that the gamma-ray therapy devices are divided into several categories based on energy and type of operation. Megavoltage therapy devices include accelerators and gamma-ray teletherapy devices such as cobalt (Co60). The Cobalt 60 is an old device and has its own disadvantages. It burns the skin in high doses because it does not protect the skin. Also, this device has penumbra due to not having a point source of radiation production. Besides, as a result of the interaction between gamma photons and the source itself, its casing, and collimators of the device, low-energy, and scattered gamma-rays are produced, and for this reason, the uniformity of the beam

Table 3. The report of pain in different head and neck regions among study populations

Questions		Initiation of therapy		During therapy		after therapy		Three months after therapy		*p-value
		No	%	No	%	No	%	No	%	
How severe was your otalgia?	Not severe	28	93.3	1	3.3	1	3.3	21	70	£0.001
	Tolerable	2	6.6	4	13.3	2	6.6	6	20	
	Severe	0	0	10	33.3	8	26.6	1	3.3	
	Excruciating	0	0	15	50	19	63.3	2	6.6	
How severe was your toothache?	Not severe	30	100	30	100	25	83.3	24	80	0.06
	Tolerable	0	0	0	0	1	3.3	1	3.3	
	Severe	0	0	0	0	2	6.6	0	0	
	Excruciating	0	0	0	0	2	6.6	5	16.6	
How severe was your mouth pain?	Not severe	20	66.6	13	43.3	10	23.3	14	46.6	£0.001
	Tolerable	4	13.3	5	16.6	7	23.3	12	40	
	Severe	5	16.6	7	23.3	8	26.6	4	13.3	
	Excruciating	1	3.3	5	16.6	5	16.6	0	0	
How severe was your jaw pain?	Not severe	20	66.6	12	40	19	63.3	20	66.6	£0.001
	Tolerable	3	10	4	13.4	7	23.3	5	16.6	
	Severe	5	16.6	2	6.6	2	6.6	4	13.3	
	Excruciating	2	6.6	12	40	2	6.6	1	3.3	
How severe was your sore throat?	Not severe	20	66.6	10	33.5	12	40	19	63.3	£0.01
	Tolerable	3	10	2	6.6	7	23.3	5	16.6	
	Severe	5	16.6	2	6.6	9	30	5	16.6	
	Excruciating	2	6.6	16	53.03	2	6.6	1	3.3	

*ANOVA, £ $p<0.05$

Table 4. The report of the effects of radiotherapy on xerostomia, mastication, trismus, and gustatory sensation in study population

Questions		Initiation of therapy		During therapy		One month after therapy		Three months after therapy		*p-value
		No	%	No	%	No	%	No	%	
How often do you feel your mouth is dry?	Never	22	73.3	15	50	2	6.6	2	6.6	£0.002
	Rarely	5	16.6	5	16.6	5	16.6	2	6.6	
	Sometimes	2	6.6	7	23.3	5	16.6	3	10	
	Mostly	1	3.3	3	10	18	60	23	80	
Do you have problem chewing?	Never	22	73.3	14	46.6	12	40	24	80	£0.01
	With hard food	6	20	11	36.6	11	36.6	3	10	
	With soft food	2	6.6	5	16.6	7	23.3	3	10	
Do you have problem swallowing?	Never	20	66.6	13	43.3	15	50	20	66.6	0.05
	With hard food	5	16.6	5	16.6	7	23.3	5	16.6	
	With soft food	2	6.6	2	6.6	4	13.3	2	6.6	
	I only can swallow liquid	2	6.6	5	16.6	2	6.6	2	6.6	
	I cannot swallow anything	1	3.3	5	16.6	2	6.6	1	3.3	
Do you have problem opening mouth?	No	20	66.6	14	46.6	12	40	19	62.7	£0.001
	To some extent	3	10	5	16.6	7	23.3	5	16.6	
	I usually have problem eating	4	13.3	5	16.6	8	26.6	5	16.6	
	I hardly can eat	2	6.6	4	13.3	2	6.6	1	3.3	
	I cannot eat	1	3.3	2	6.6	1	3.3	0	0	
Has your sense of taste changed?	Never	20	66.6	13	43.3	15	50	20	66.6	£0.01
	Mildly	5	16.6	5	16.6	7	23.3	5	16.6	
	Moderately	2	6.6	2	6.6	4	13.3	2	6.6	
	Severely	2	6.6	5	16.6	2	6.6	2	6.6	
Has your voice become harsh?	Never	25	83.3	20	66.6	21	70	26	89.9	0.05
	To some extent	2	6.6	0	0	2	6.6	2	6.6	
	Sometimes	2	6.6	5	16.6	3	10	3	10	
	All the time	1	3.3	5	16.6	1	3.3	0	0	
Have you recently had loss of hearing?	Yes	5	16.6	10	33.3	8	26.6	3	10	0.07
	No	25	83.3	20	66.6	22	73.3	27	90	

*ANOVA, £ $p<0.05$

is slightly reduced. Therefore, it seems that the side effects caused by radiotherapy can be minimized by using new devices (20,21).

Conclusion

Following one month of therapy, these adverse effects reach their maximum rate, and from then until the end of the third month after treatment, they continue to improve until they approach near to their pre-treatment levels.

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Ethics

Ethics Committee Approval: This project was approved by the Ethical Committee of Kerman University of Medical Sciences of the university with the code IR.KMU.REC.1399.488 (date: 17.08.2023).

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Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A.H., Design: M.A.H., Data Collection or Processing: A.E., A.R.G.N., Analysis or Interpretation: A.R., Literature Search: A.R., Writing: A.R.G.N.

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Original Article / Özgün Araştırma

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Evaluation of The Efficacy, Side Effects, and Drug Survival Data with Methotrexate-leflunomide Combination Therapy in Patients with Inflammatory Arthritis

Enflamatuvar Artritli Hastalarda, Metotreksat-leflünomid Kombinasyon Tedavisi ile Etkinlik, Yan Etki ve İlaçta Kalım Verilerinin Değerlendirilmesi

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Abstract

Objective: Conventional synthetic disease-modifying antirheumatic drugs are used alone or in combination to treat inflammatory arthritis. The risk of serious side effects may also increase with the combination of methotrexate and leflunomide (MTX + LEF), which is used for better clinical response.

Materials and Methods: The data of 107 patients who received MTX + LEF treatment for inflammatory arthritis were retrospectively reviewed.

Results: The mean age was 50 (±13), and the median disease duration was five years. Three months after the initiation of MTX + LEF treatment, 76.6% of patients continued treatment in remission. The mean duration of drug survival for these patients was 30 months. The most important reasons for drug discontinuation in the first three months after treatment initiation were primary inefficacy and >2-fold increase in transaminases, whereas remission, patient decision, or secondary non-response were found in long-term follow-up. The frequency of transaminase elevations was 9.3% (10/107), and 70% of these were observed in the first three months of treatment, and all resolved after drug discontinuation. The incidence of serious infections was 6.5% (7/107), and mortality was not observed; the incidence of serious infections was higher in the elderly (p=0.002). The MTX + LEF continuation rate was 45% at the last visit of the patients included in the study.

Conclusion: The MTX + LEF combination is a safe and effective option for achieving remission when used considering old age and comorbidities; It is important to closely monitor transaminase levels, especially in the first three months.

Keywords: Arthritis, methotrexate, leflunomide combination, efficacy, side effects

Öz

Amaç: Enflamatuvar artrit tedavisinde konvansiyonel sentetik hastalık modifiye edici antiromatizmal ilaçlar tek başına veya kombinasyon halinde kullanılmaktadır. Daha iyi klinik yanıt için kullanılan metotreksat ve leflunomid (MTX + LEF) kombinasyonu ile ciddi yan etki riski de artabilir.

Gereç ve Yöntemler: Çalışmamızda enflamatuvar artrit nedeniyle MTX + LEF tedavisi alan 107 hastanın verileri retrospektif olarak incelendi.

Bulgular: Ortalama yaş 50 (±13), ortanca hastalık süresi 5 yıldı. MTX + LEF tedavisi başladıktan 3 ay sonra hastaların %76,6'sı remisyonda tedaviye devam etti. Bu hastalar için ortalama ilaç kullanım süresi 30 ay saptandı. Tedavi başlangıcından sonraki dönemde ilk üç ay içinde ilaç kesilmesinin en önemli nedenleri birincil etkisizlik ve transaminazlarda >2 kat artış iken, uzun dönem takiplerde ilaç kesilmesinin nedenleri ise remisyon, hasta kararı veya sekonder yanıtsızlık olarak saptandı. Transaminaz yükselmelerinin sıklığı %9,3 (10/107) idi ve bunların %70'i tedavinin ilk üç ayında gözlendi ve tümü ilaç kesildikten sonra düzeldi. Ciddi enfeksiyon sıklığı %6,5 (7/107) olup, mortalite gözlenmedi, ciddi enfeksiyon sıklığı yaşlılıkta daha fazlaydı (p=0,002). Hiçbir hastamızda tedaviye bağlı mortalite görülmedi. Çalışmaya alınan hastaların son vizitte MTX + LEF devam oranı %45 bulundu.

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Sonuç: MTX + LEF kombinasyonu yaşlılık ve komorbiditeler dikkate alınarak kullanıldığında remisyon sağlamada güvenli ve etkili bir seçenektir; özellikle ilk 3 ay transaminaz düzeylerinin yakından izlenmesi önemlidir.

Anahtar Kelimeler: Artrit, metotreksat, leflunomid kombinasyon, etkinlik, yan etki

Introduction

Most treatment guidelines and recommendations recommend methotrexate (MTX) and conventional disease-modifying antirheumatic drugs (csDMARDs) alone or in combination as first-line treatment for inflammatory arthritis. These drugs are advantageous treatment options due to their low risk, cost profile, and mostly oral use.

MTX, a structural analog of folic acid, acts by suppressing inflammation mediated by adenosine increases. Although most of the common side effects with MTX are mild and do not require discontinuation of the drug, serious side effects such as hepatotoxicity, pulmonary toxicity, infections, and myelosuppression can be seen rarely as treatment complications (1). Risk factors for pulmonary toxicity are the presence of diabetes, advanced age, rheumatoid lung involvement, and hypoalbuminemia (2-5). Risk factors for hepatotoxicity are untreated hepatitis B and C infection, not using folic acid, obesity, hyperlipidemia, hepatosteatosis, alcohol consumption, and high doses of MTX (2-6). Risk factors for hematological side effects are MTX overdose, inadvertent daily use of the drug, renal failure, hypoalbuminemia, and concomitant use of trimethoprim/sulfamethoxazole (3,4). Despite these infrequent serious side effects, MTX has a very good safety profile with appropriate patient selection, education, and follow-up.

Leflunomide (LEF) is an immunomodulatory agent which works by blocking T-cell proliferation by inhibiting pyrimidine synthesis. The most common side effects are gastrointestinal symptoms (cramps and diarrhea) and hepatotoxicity (1). Interstitial lung disease with LEF is a rare but serious pulmonary complication with high mortality. Concomitant use of LEF and MTX raises concerns about hepatotoxicity, bone marrow suppression, pneumonitis, and risk of infection (1,6-9).

In this study, we aim to retrospectively evaluate patients treated with MTX + LEF in clinical practice and to obtain real-world data regarding efficacy, safety, and adverse events.

Materials and Methods

This is a single-center, retrospective, and observational study. This study was approved by the Bakırçay University Faculty of Medicine Research Ethics Committee after reviewing the ethical issues (decision no: 1044, date: 17.05.2023). Between January 2011 and October 2022, 107 patients who received combination MTX + LEF treatment for inflammatory peripheral arthritis in İzmir University of Economics Medical Point Hospital Rheumatology Clinic were included in the study. The patients included in the study were selected from patients over 18 years of age with rheumatoid arthritis (RA), psoriatic arthritis (PsA), undifferentiated spondylarthritis (uSPA), and undifferentiated connective tissue disease (uCTD). None of the patients had regular alcohol use, known interstitial lung disease, or hepatitis B and C infections. Patients with drug incompatibility and not attending follow-up were excluded from the study. Of the patients included in the study, 75 were diagnosed with RA according to the 2010 RA classification criteria (10), and 23 were diagnosed with PsA according to the classification of psoriatic arthritis criteria (11). Of the other patients with inflammatory arthritis included in the study, five were diagnosed with uSPA and four with uCTD.

The data of the patients were obtained from computer records These records included patient complaints, tender and swollen joint counts, physical examination findings, acute phase responses, routine complete blood counts and biochemical parameters, and, if any, other detailed additional tests required at that visit.

Statistical Analysis

IBM SPSS 21.0 program was used for statistical analysis. Descriptive statistical methods were used to evaluate the data. Pearson correlation test in determining the linear relationship of quantitative variables; Spearman's correlation test was used to evaluate ordinal variables. The chi-square test was used when comparing the qualitative variables of two independent groups. The statistical significance value was taken as $p<0.05$.

Results

Demographic data of 107 patients included in the study is given in Table 1. 70% of patients were women. (male/female: 30/77) The mean age of the patients was 50 (±13) years, and 44% of the patients had additional diseases such as hypertension, diabetes mellitus, thyroid disease, chronic obstructive pulmonary disease, coronary artery disease, and insulin resistance. The median duration of the disease was five years (1-39 years). 70% of the patients included in the study were diagnosed with RA, 21% were diagnosed with PsA, and the remaining patients were diagnosed with uCTD and uSPA.

Patients who were followed up for at least three months after initiating the MTX + LEF combination were included in the study. The median time to initiate the MTX + LEF combination in our patients was 24 months.

Remission was defined as no tender or swollen joints on examination of 51 joints (12) and normal acute phase

responses. The presence of active arthritis was evaluated as a clinical ineffectiveness.

Survival in MTX + LEF combination therapy:

Although the follow-up processes of the patients were different, drug survival rates were evaluated considering the drugs used at the last visit.

In the 3rd month of MTX + LEF treatment, 76.6% of the patients (82/107 patients) were able to continue the treatment in remission. These patients' mean duration of drug survival at follow-up was 30 months. The rate of patients who were continuing MTX + LEF treatment at their last visit at the time of the study analyses was 45% (Table 1).

MTX + LEF combination discontinuation:

After MTX + LEF treatment was started, combination therapy was discontinued in 55% (59 patients) of the patients for various reasons. 42% of drug discontinuations occurred within the first three months.

In these patients whose treatment was discontinued within the first three months (25/107), the reasons for discontinuation were adverse events in 16 patients and primary clinical ineffectiveness in 9 patients (Table 2).

The main reasons for discontinuing the treatment during the follow-up period in patients who are in remission and continue their medication as of the third-month visits (82/107) are; secondary ineffectiveness or patients left on their own because of their well-being or concerns (Table 2).

Side effects of MTX + LEF combination therapy:

Side effects that led to drug discontinuation in the first three months were found to be >2 times higher transaminases in 7 of the patients, serious infection in 3, and diarrhea, alopecia, and skin rash in 6 of them.

While the frequency of transaminase elevation >2 times higher in the whole group was 9.3% (10/107), this side effect occurred in 70% of the patients in the first three months of treatment, and advanced age did not have a negative effect in this regard (p>0.05).

The rate of serious infection in the whole group was found to be 6.5% (7/107). Three of these infections were seen in the first three months. Of the seven serious infections in our patients, 4 were pneumonia, 1 was intra-abdominal and 2 were urinary tract infections. Hospitalization was required in 3 patients, and all patients recovered with treatment. A significant correlation was found between advanced age and serious infection (*r* spearman=0.299 p=0.002). Comorbidity was present in 5 of 7 patients with severe infection.

Clinical efficacy:

MTX + LEF combination therapy was discontinued in 19 (17%) of patients due to ineffectiveness. While 9 of these patients were primary unresponsive, 10 were secondary non-responders.

In our study, no correlation was found between rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibody (anti-CCP) positivity and the effectiveness of combination therapy (*r* pearson=-0.031 p=0.07 and *r* pearson=-0.006 p=0.96 respectively). Drug discontinuation rates did not differ according to the diagnosis of the patients (p>0.05).

Table 1. Demographic data of the patients included in the study

Total (n)	107
Female/male (n)	77/30
Mean age (years)	50 (±13)
Disease duration (years)	median: 5 (1-39)
Diagnosis (number of patients)	
RA	75
PsA	23
uCTD	5
uSPA	4
Drug survival at the last visit (number of patients)	48(44.5%)
Comorbidities (number of patients) (DM, HT, COPD, thyroid, CAD)	48(44.5%)

RA: Rheumatoid arthritis, PSA: Psoriatic arthritis, uCTD: Undifferentiated connective tissue disease, uSPA: Undifferentiated spondyloarthritis, DM: Diabetes mellitus, HT: Hypertension, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease

Table 2. Drug discontinuation and side-effect data in patients receiving MTX + LEF combination

	>2x transaminase elevation	Severe infections (n)	Intolerant (n)	Quit by their own decision	Non-responders
Discontinued in the first 3 months (n=25) 42%	7	3	6	-	9 (primary ineffectiveness)
Discontinued in the follow-up period (n=34) 58%	3	4	6	11	10 (secondary loss of response)
Total (n=59)	10	7	12	11	19

MTX: Methotrexate, LEF: Leflunomide

Discussion

This is a study examining the efficacy and safety of the MTX + LEF combination in inflammatory arthritis based on real-life data. In our study, the data of 107 patients who were followed up by our rheumatology outpatient clinic and received combination therapy for a period of 10 years were analyzed retrospectively. In our results, the rate of >2 times transaminase elevation, which is one of the important treatment-related side effects, was found to be 9.5%, and 70% were recorded within the first three months. As of the 3rd month of the treatment, the rate of patients who tolerated the treatment and were in remission was 76%, and the median drug survival was 30 months in these patients. The frequency of serious infection was 6.5%, and a significantly increased correlation was found between advanced age and the risk of serious infection. No treatment-related mortality was observed in our patients. During the long-term follow-up, the main factors for discontinuation of combination therapy were secondary loss of response or the patient's desire to discontinue one of the drugs while in remission.

Although the rates of transaminase elevations observed with MTX and LEF were reported to be between 5.4-16.3% in randomized controlled studies, the rate of transaminase elevation was found to be 31% in patients with PsA, alcohol use, and higher doses of MTX, in the study of Curtis et al. (3,8,13-15). Alves et al. (16), in a series of 71 RA patients, showed that there was no difference between MTX monotherapy and MTX + LEF combination in terms of transaminase elevation. In our study, the frequency of >2-fold elevation of transaminases was found to be 9.5%, and 70% was observed within the first three months. In our study, transaminase elevation did not differ in patients with RA or PsA. Patients with alcohol use or chronic liver disease were not already given combination therapy, and MTX doses were not included in our analyses.

In a series of 194 patients examining the data of the MTX + LEF combination, six patients had serious infections, and 2 of these infections resulted in death, while other infections were reported as sepsis in 3 patients and tuberculosis in 1 patient (17). In our patients, 3 of 7 serious infections required hospitalization, and all patients recovered with treatment. Patients who developed serious infections were predominantly elderly patients, and this relationship between increasing age and infection was found to be statistically significant.

In a multicenter study, data from 1671 RA patients were analyzed. Patients were grouped according to treatments as follows: MTF + LEF combination; MTX alone; LEF alone; or MTX/LEF + biological DMARD/Janus kinase inhibitor (JAKi). While the side effects seen with the MTF + LEF combination were similar to the patients who received MTX or LEF alone, the risk of serious side effects and risk of infection was found to be lower than those who received biological DMARD/JAKi + MTX/LEF (18).

In a study of 120 RA patients, the group receiving MTX + LEF combination was compared with the group receiving only MTX, adverse reaction rates were found to be similar, while both clinical and acute phase responses were found to be better in the group receiving MTX + LEF. Interleukin-1 and tumor necrosis factor-alpha levels were also found to be lower in this group (19). In another study retrospectively examining the data of 91 patients receiving the MTX + LEF combination and 22 patients receiving LEF alone, The efficacy of the MTX + LEF combination was not found to be superior to those who received LEF alone. In this study, no difference was found in terms of side effects (20).

In a study of RA patients with inadequate response to MTX monotherapy in China, patients were randomized into two groups, either MTX + LEF or MTX + hydroxychloroquine (HQ). MTX + HQ group was found to be superior in this cohort of two years of real-world data (21). The safety profiles were not of concern, and there were no significant differences between the two groups.

In another study, the results of 45 PsA patients who were unresponsive to MTX monotherapy and switched to the MTX + LEF combination was evaluated, and it was found that only 7 of these patients had to switch to biological DMARDs during follow-up. The reasons for the treatment change in these seven patients were determined as MTX + LEF ineffectiveness and hepatotoxicity. The authors reported that this combination was well tolerated, and drug survival was very good. 84% of patients were continuing with MTX + LEF at the time the study ended (22). In our study, the rate of patients continuing MTX + LEF treatment at the last visit was 45%, and the median drug survival was 30 months.

Most of the studies in the literature are observational and retrospective. Factors such as the short follow-up period of the patients, the heterogeneity of the doses of MTX and LEF used in combination therapy, the doses of corticosteroids used together, the comorbidities and the lack of data on other concomitant drugs are the main limitations of these studies. The COMPLETE-PsA trial was a randomized, placebo-controlled, double-blind clinical trial. This study will provide important information for treatment strategies and recommendations (23).

In our study, the lack of a control group and drug doses were limiting factors. On the other hand, it is valuable in terms of having the longest follow-up period compared to other studies, the effect of additional diseases on side effects, and comparing the results in different disease groups.

Conclusion

In conclusion, the combination of MTX + LEF appears to be an effective and safe treatment option in patients with both RA, PsA, uSpa, and uCTD. These results are important in reassuring physicians and patients, especially in low-budget countries, when the transition to bDMARD needs to be postponed to the next steps due to the health system policies of countries or various conditions.

Our study suggests that patients with advanced age and additional disease should be more careful in terms of infection risk and that patients should be followed more frequently in terms of hepatotoxicity, especially in the first three months.

Ethics

Ethics Committee Approval: This study was approved by the Bakırçay University Faculty of Medicine Research Ethics Committee after reviewing the ethical issues (decision no: 1044, date: 17.05.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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Original Article / Özgün Araştırma

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Mechanical Effects of Different Femoral Stem Diameters of Distal Tumor Prosthesis on Femoral Cortex

Distal Tümör Protezlerinde Farklı Femoral Stem Çaplarının Femoral Korteks Üzerindeki Mekanik Etkileri

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Abstract

Objective: Distal femur tumor prostheses are often used in tumor surgery. One of the critical complications of these prostheses is the insufficiency of stems. The stems are used on several orthopedic implants to provide stability and strength to the bone-implant connection. This study aimed to determine the mechanical effects of the stem diameter on tumor prostheses.

Materials and Methods: Finite element analysis was performed on three distal femur tumor prosthesis designs implanted in the femur with different stem diameters (12, 14 and 15 mm) with the same stem length of 140 mm. A statically axial compression load of 800 N was applied to the femur, and stress values on the stems and femoral cortexes were calculated and compared.

Results: The stress measurements on the femur shaft were 49.289, 48.987 MPa and 45.424 MPa for stem diameters of 12, 13 and 15 mm, respectively, and on the distal portion of the femur were 61.205, 59.39 MPa and 52.526 MPa. For each diameter, the proximal stems had 301.24 MPa, 273.84 MPa, and 228.19 MPa stress values, whereas the distal stems had 365.49 MPa, 305.91 MPa and 275.41 MPa for diameters of 12, 14, and 15 mm.

Conclusion: Finite element model analysis indicated that when the stem diameter increases, the maximum stresses on the femoral cortex and stem decrease.

Keywords: Finite element analysis, stem diameter, tumor prosthesis

Öz

Amaç: Distal femur tümör protezleri tümör cerrahisinde sıklıkla kullanılmaktadır. Bu protezlerin kritik komplikasyonlarından biri de stemlerin yetersizliğidir. Protezin stem (sap) kısımları, kemik-implant bağlantısına stabilite ve güç sağlamak için çeşitli ortopedik implantlarda kullanılır. Bu çalışma, stem çapının tümör protezleri üzerindeki mekanik etkilerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Farklı gövde çaplarına (12, 14 ve 15 mm) ve aynı gövde uzunluğu 140 mm'ye sahip femura implante edilmiş üç distal femur tümör protezi tasarımına sonlu elemanlar analizi gerçekleştirildi. 800N statik eksenel kompresyon yükü femura uygulandı ve stemler ile femoral korteksler üzerindeki stres değerleri hesaplandı ve karşılaştırıldı. Femura 800N statik eksenel yük uygulanarak stemler ve femoral korteksler üzerindeki stress değerleri hesaplandı ve karşılaştırıldı.

Bulgular: Femur şaftındaki stres ölçüm değerleri, 12 mm, 13 mm ve 15 mm gövde çapları için sırasıyla 49.289 MPa, 48.987 MPa ve 45.424 MPa ve femurun distal kısmında 61.205 MPa, 59.39 MPa ve 52.526 MPa'dır. Her bir çap için stemlerin proksimali 301.24 MPa, 273.84 MPa ve 228.19 MPa stres değerlerine sahipken, stemlerin distalleri 12, 14 ve 15 mm çaplar için 365.49 MPa, 305.91 MPa ve 275.41 MPa stres değerlerine sahiptir.

Sonuç: Sonlu elemanlar analizi, stem çapı arttıkça femoral korteks ve stem üzerindeki maksimum stres değerlerinin azaldığını göstermiştir.

Anahtar Kelimeler: Sonlu elemanlar analizi, stem çapı, tümör protezi

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Introduction

Extremity-saving surgery to treat bone and muscle tumors has frequently become applicable through advanced surgery techniques last 20 years (1). Tumor prostheses are used on revision knee and lower extremity saving surgery, unstable knees due to the damage of ligaments and tumor resections (1-3).

Endoprosthesis reconstruction has recently become a more common alternative to allograft or autograft in limb salvage procedures (4,5). The limb salvage operation usually necessitates extensive dissection in a poor medical condition host (5,6). In addition to the increased stress caused by the endoprosthesis, limited soft tissue support and constraint following the limb salvage procedure usually result in increased complications, particularly in long-term survivors (7,8).

Stems are used on several types of orthopedic implants to provide stability and strength to the bone-implant connection (9,10). The load transfer between the implant and the cortical bone is essential for implants with intramedullary stems (11-13). Implant-to-bone load transfer is affected by the implant's geometry and design in the resected bone surface area that typically separates the extramedullary and intramedullary portions of the implant (14,15).

Finite element analysis (FEA) is now the most used technique for analyzing physical phenomena in structural, solid and fluid mechanics, biomedicine, biomechanics, and orthopedics (9,16). FEA conducts analyses in two dimensions and three dimensions, linear and non-linear, static and dynamic ranges, and stress and strain fields on bones and prostheses to determine whether bones or parts of the skeleton are healthy or diseased. The models created and used for FEA should be sufficiently refined to accurately represent the geometry and mechanical behavior of the bone structure they simulate (17-19).

In this study, we aimed to determine the stress values on the femur and the stem at different stem diameters using FEA and to figure out the optimum stem diameter for the tumor prosthesis.

Materials and Methods

A FEA was undertaken on a simplified 3D model of a tumor prosthesis with cylindrical glossy surfaces. A composite human femur's computed tomography scan created a solid femur model having 45 mm head diameter, 4 mm cortex thickness and 390 mm length from the proximal tip. And the 3D model of a distal femur hinged type tumor prosthesis was created with a modeling package of Autodesk Inventor Professional (Autodesk, San Rafael, California) and NX (Siemens Digital Industries Software, Plano, TX) software programs. The prosthesis is modeled with different stem diameters (12-14 and 15 mm) and all with a length of 140 mm. FEA was conducted to determine the bone and stem stress patterns with ANSYS Workbench software (ANSYS, Inc. Canonsburg, PA). The prosthesis was modeled using isotropic material properties for stainless steel 316 L. And the bone elements were assigned transverse isotropic cortical bone properties;

Cortical Bone: E:18,2 GPa - poison rate: 0.33

Stainless Steel: E: 193 GPa - poison rate: 0.31

The prosthesis was virtually implanted in the femur and the model was fully constrained against movement toward the distal end of the prosthesis (Figure 1). An axial load of 800N was statically applied to the head of the femur with 20° angles (oblique load) to its long axis to simulate the anatomic conditions. Stress distributions on the stem and femoral cortex resulted from static finite element analyses and were compared in all cases.

The current research does not require ethical approval as it involves no tissue and/or human material.

Statistical Analysis

FEA is made in 3D models, so the properties of the sample entered in the computer do not change. In our study, only one prosthesis model is used, and material properties are the same, so statistical analysis is not performed.

Results

Long-term results show advanced prosthesis loosening due to stress, as shown in theoretical biomechanical investigations (20,21). The risk of aseptic loosening rises and the surrounding bone is stress-shielded. It's

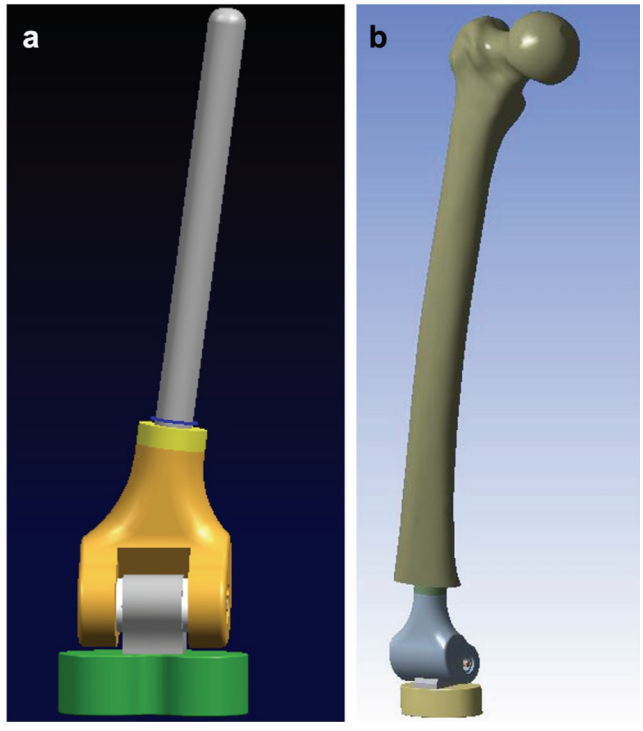

Figure 1. **(a)** 3D model of a prosthesis and **(b)** tumor prosthesis on bone

interesting to note that studies rarely attribute aseptic loosening to prosthetic design. Surprisingly, studies hardly ever link prosthetic design to aseptic loosening. The aseptic loosening processes for large tumor prostheses are probably similar to those in conventional total joint arthroplasty. They are connected to bone adaptation following changes in stress patterns. The different force orientations can subject the prosthesis to torsional, compression, shearing, and tension stress. Our FEA results indicated that the stress measurements on the femur shaft are 49.289 MPa, 48.987 MPa and 45.424 MPa for the stem diameters of 12 mm, 13 mm, and 15 mm respectively and on the distal portion of the femur is 61.205 MPa, 59.39 MPa and 52.526 MPa. For each diameter, the proximal stems have 301.24 MPa, 273.84 MPA and 228.19 MPa stress values while the distal stems having 365.49 MPa, 305.91 MPa and 275.41 MPa for the diameters of 12, 14 and 15 mm (Figure 2). And also the maximum Von-Mises stress values and locations can be seen on Figure 3.

Discussion

The limp salvage procedure is preferred for treating bone tumors. The tumor prosthesis is used to reconstruct the skeletal system many reports in the literature concerning the performance of massive distal femoral replacements (22,23). The prosthetic stem problems are primarily seen in bone tumor treatment. Common complications include wound problems, infection, aseptic loosening, fatigue fracture, dislocation/subluxation and mechanical failure (24,25).

Knowing the biomechanical characteristics of tumor prosthesis will clinically prevent most complications, especially insufficiency of implants. Transferring the load to the prosthesis and bones regularly makes having a more prosperous and long-lived prosthesis possible.

Aseptic loosening is primarily caused by increased local stress at the bone-cement and cement-prosthesis interfaces. Other factors that contribute include direct stress and increased local bending force. Shielding after extensive soft tissue resection is one cause of increased local stress. Other causes include biological local osteolysis response to wear particle disease, infection-induced granulation tissue accumulation, and wide excision of soft tissue, which reduces soft tissue constraints to compensate for torsion.

Transitioning from an early single axial fixed-hinge knee endoprosthesis to a rotation-hinged knee prosthesis dramatically reduced aseptic loosening. There are some finite element model (FEM) studies about different tumor prostheses to determine the effects of stem designs and sizes on stress distribution at the bone and the prosthesis. The FEM results showed increasing peak cancellous stress and decreasing average proximal cancellous stress with increasing stem length. A longer stem increased the load transfer and improved the implant's stability. The amount of unloaded surrounding bone increases near the insertion level as fixation length increases. This stress shielding may cause atrophy and finally lead to aseptic loosening. Aseptic loosening is the predominant cause of failure of distal femoral replacements.

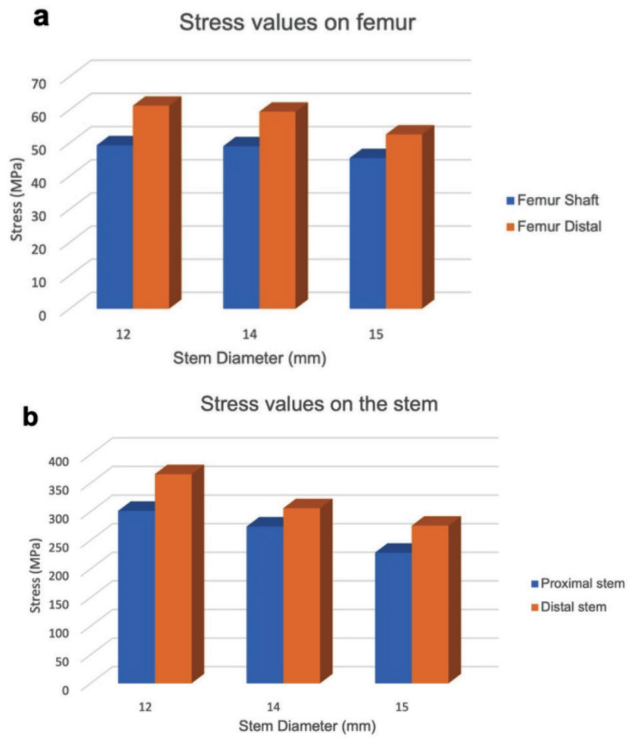

Figure 2. Stress values on **(a)** femur and **(b)** stem

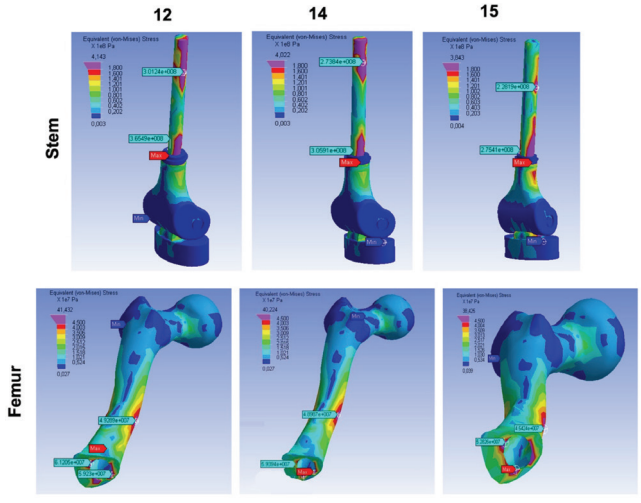

Figure 3. The finite element analysis on each diameter of the femur's stem and proximal medial cortex

Conclusion

There are studies on stem diameters about the effects of stem diameters on bone-prosthesis systems. The effect of stem size on aseptic loosening and the rate of stem filling of the bone canal and durability are directly related. We think that stem diameter is a critical issue affecting the femur's stress distribution. To know the impact of stem diameter, we intended to make FEA on femur models. In this study, it is determined that increasing the diameter of the stem decreases the stresses at the femur cortex and stem of the prosthesis. When the diameter of the femoral stem is increased to the optimum value that the bone structure allows, it can be possible to reduce the stresses to the minimum levels.

Ethics

Ethics Committee Approval: The current research does not require ethical approval as it involves no tissue and/or human material.

Informed Consent: This study does not require informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.U., B.Ç., Design: B.U., Data Collection or Processing: B.U., Analysis or Interpretation: B.U., B.Ç., Literature Search: B.Ç., Writing: B.U., B.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Recurrent Presentations to the Emergency Department During the COVID-19 Pandemic

COVID-19 Pandemi Döneminde Acil Servise Yapılan Tekrarlayan Başvuruların Değerlendirilmesi

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Abstract

Objective: Coronavirus disease-2019 has resulted in changes in healthcare and management services. One of these changes is related to in patient presentation to emergency departments (ED). This study aimed to investigate the rate of recurrent presentations to an ED during the pandemic period compared to the pre-pandemic period.

Materials and Methods: Patients that presented to the ED of a tertiary hospital again within 72 hours of their first visit were screened from the hospital information management system for the pre pandemic (June 1-November 30, 2019) and pandemic (June 1-November 30, 2020) periods. So, hospitalization rates were compared between the two periods.

Results: In the pre-pandemic period, the number of ED registrations was 67,414, of which 3,463 belonged to recurrent presentations, while in the pandemic period, these numbers were determined as 43,636 and 2,238, respectively. The rate of admission to any hospital ward (n=521, 16.4%) or the intensive care unit (n=56, 1.8%) nearly doubled during the pandemic. Six of these patients died in the ED in the pandemic period, while no death was observed in the pre-pandemic period.

Conclusion: Although there was a decrease in the number of both hospital and ED presentations during the pandemic, an increase was observed in the number of patients with recurrent presentations to the ED. As a result of this patient group postponing visits to the hospital for their acute problems due to the fear of being infected, their need for hospitalization and intensive care follow-up increased.

Keywords: Pandemic, recurrent presentation, emergency department, COVID-19

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) sağlık bakım ve yönetim hizmetlerinde değişikliklere neden oldu. Bu değişikliklerden biri de acil servis hasta başvurularında yaşandı. Bu çalışmada pandemi döneminde acil servislerde tekrarlayan başvuru oranlarının araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Pandemi öncesi dönem (1 Haziran-30 Kasım 2019) ile pandemi döneminde (1 Haziran -30 Kasım 2020) 3. basamak bir hastanenin acil servisine ilk başvuru sonrası 72 saat içerisinde tekrar başvuruda bulunan hastalar hastane bilgi yönetimi sistemi üzerinden taranmıştır. Hastane ve acil servis başvuru sayıları, demografik özellikleri ve hastaneye yatış oranları her iki dönem açısından karşılaştırılmıştır.

Bulgular: Pandemi öncesi dönemde acil servis kayıt sayısı 67.414 olup bu hastalar içerisinde 3.463'ü tekrarlayan başvuruyken, pandemi döneminde kayıt sayısı 43.636 olup bunların 2.238'i tekrarlayan başvuruda bulunmuştur. Dönemler arasında istatistiksel olarak yaş ve cinsiyet açısından farklılık tespit edilmemiştir (p=0,143). Ancak tekrar başvuruda bulunan hastalar arasında yatarak takip ve tedavi edilmesi gereken hasta grubunun yaşı pandemi döneminde daha yüksekti. Pandemi döneminde herhangi bir kliniğe (n=521, %16,4) veya yoğun bakım ünitesine yatış (n=56, %1,8) oranlarında yaklaşık iki kat artış oldu. Bu hastalardan 6'sı pandemi döneminde acil serviste ölümle sonlanıma sahipken normal dönemde ölümle sonlanım görülmemiştir.

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Sonuç: Pandemi döneminde hem genel hastane hem de acil servis başvuru sayılarında azalma olmasına rağmen acil servise tekrarlayan başvuruda bulunan hasta sayısında artış olduğu tespit edildi. Bu hasta grubunun enfekte olma korkusu nedeniyle akut gelişen problemlerini ertelemesi karşısında herhangi bir kliniğe yatış ve yoğun bakım ünitesinde takip edilme ihtiyaçlarının artığı görüldü.

Anahtar Kelimeler: Pandemi, tekrarlayan başvuru, acil servis, COVID-19

Introduction

Coronavirus disease-2019 (COVID-19) pandemic, which has affected the whole world, has resulted in difficulties in healthcare provision and management services, requiring the restructuring of the health system. While focusing on providing the best medical care for people with COVID-19, healthcare services also aimed to protect people that wanted to receive healthcare against this infection (1). This situation reduced patients' demand for outpatient services due to their reservations concerning the risk of transmission, but it also transformed emergency departments (EDs) into areas considered by patients as primary choices in the presence of any medical problem since they provide healthcare service 24 hours a day for seven days a week.

A recurrent presentation is a patient presenting to an ED with the same or a different complaint within 72 hours after his/her first discharge (2). Recurrent visits have been identified as quality indicators for patient care and safety in EDs across the world (3). Although these presentations generally vary from one country to another and on a regional basis, global data indicate that 3% is an acceptable rate for recurrent ED presentations (4). This generally depends on the demographic characteristics of patients, their comorbidities, course and severity of their existing diseases, adequacy of treatment, and many factors originating from the physician (2,5,6). It is considered that many changes prompted by the pandemic, decreased outpatient services, postponement of scheduled surgical services, ineffective homecare services, and patients and/or their relatives not accepting hospitalization may have increased the number of recurrent presentations to EDs during this period.

This study aimed to investigate the rate and characteristics of recurrent presentations to an ED during the pandemic period compared to the pre-pandemic period.

Materials and Methods

This study was a retrospective analysis of patients that presented to the ED of a tertiary care hospital during the pandemic period from June 1, 2020, through November 30, 2020, and during the same time one year earlier representing the pre-pandemic period (June 1, 2019-November 30, 2019). Approval for the study was obtained from the Recep Tayyip Erdoğan University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision number: 2021/69, date: 08.04.2021).

Study Design

This study was planned retrospectively using the data obtained from the hospital information management system (HIMS). The ED where the study was conducted receives 140,000 patient admissions annually and can provide acute care in all specialties. During the pandemic, all the hospitals in the province provided medical care and treatment services for all patients, including those with COVID-19.

Study Data

Hospital presentations included all consecutive patients that visited the hospital for any reason to receive healthcare. ED visits included patients that presented to ED within 24 hours and were registered in HIMS. Based on the date of March 11, 2020, when the first case of COVID-19 was reported in Turkey, patient presentations to ED from June 01, 2020, through November 30, 2020, were considered as 'pandemic presentations', and those that were made during the same date range one year earlier (June 1, 2019- November 30, 2019) were considered as 'pre-pandemic presentations'. The repeated presentations of the same patients due to any complaint within 72 hours after their first ED visits were defined as 'recurrent presentations' (2). The data of the study population, presentation date, presentation complaint, hospital unit where treatment was provided, and outcomes were recorded in the study form according to the specified study intervals.

Patient Selection

Among the patients aged 18 years and over who visited ED within the specified date range, those with recurrent presentations applied again within 72 hours after their first presentations were included in the study. Patients that were called for a control following a previous visit and those that were referred by law enforcement officers for procedures, such as examinations, hospitalization, dressing, catheter change, injection, or forensic control were excluded from the study.

Statistical Analysis

In this study, the distribution of continuous data was evaluated with histogram graphs and the Shapiro-Wilk test. Mean and standard deviation values were reported for parametric data, and median and interquartile range (IQR) values for non-parametric data. For categorical data, number (n) and frequency (%) values were used. For the comparison of data between two independent groups, Student's t-test, Mann-Whitney U test, or Pearson's x^2 test was applied. Moreover, odds rations (OR) with 95%

confidence intervals (95% CI) were calculated to achieve predictive odds of mortality among pandemic and pre-pandemic periods. In all the statistical analyses, $p<0.05$ was considered statistically significant, and analyses were performed using R-based Jamovi statistical software [The Jamovi Project (2021), version 2.3].

Results

The study was conducted with 3,184 patients that met the inclusion criteria. During the pandemic period, there was a 35% decrease in ED presentations. Although there was a 42% decrease in recurrent presentations to ED, 3% of ED presentations in both periods consisted of recurrent presentations (Figure 1).

Considering the gender distribution of the patients with recurrent presentations according to the period, no statistically significant difference was found, although the rate of female patients was lower (p=0.153). The mean age of the patients with recurrent presentations was 51 (IQR: 36-65) years during the pre-pandemic period and 54 (IQR: 37-67) during the pandemic period, indicating a significant difference (p=0.0250).

When ED outcomes were evaluated, the number of patients that required hospitalization was 284 (14.1%) during the pre-pandemic period and 299 (25.6%) during the pandemic period. Among the patients with recurrent representations, the need for hospitalization nearly doubled during the pandemic ($p<0.001$). In this patient group, the median age was 62 (IQR: 45-74) years, while the median age of the discharged patients was 50 (IQR: 35-64) years ($p<0.001$). No significant difference was found between these two groups in terms of gender.

In the group requiring hospitalization, the need for admission to the intensive care unit was observed in 28 (1.39%) patients in the pre-pandemic period and 34 (2.9%) patients during the pandemic. The rate of intensive care unit admissions nearly doubled among the patients with recurrent presentations during the pandemic (p=0.003). The median age of these patients was 67 (IQR: 55-77.8) years, and the median age of patients without the need for follow-up and treatment in the intensive care unit was 51 (IQR: 36-66) years, with a statistically significant difference being found between these two groups in relation to age ($p<0.001$). There was also no statistically significant difference between these patients in terms of gender (p=0.008).

Six of the patients with recurrent presentations (0.5%) died in ED during the pandemic period, while no death was observed in ED during the pre-pandemic period ($p<0.001$). It was determined that the probability of mortality increased 22.6 times in recurrent presentations during the pandemic period (OR: 22.60, 95% CI: 1.27-401). A statistical analysis could not be performed due to the low number of patients that died. However, the patients in this group were of advanced age, with their median age being calculated as 74.5 (IQR: 64.3-82.5) years (Table 1).

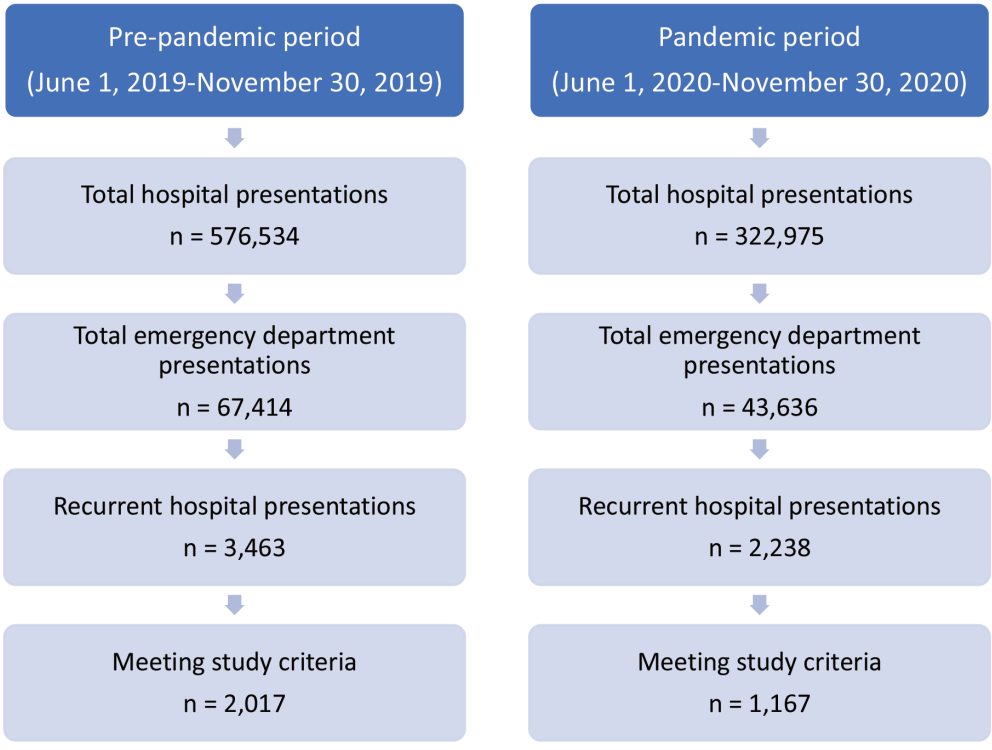

Figure 1. Flow chart of the study

Table 1. Emergency department outcomes of the patients according to the presentation period				
Period	Pre-pandemic (2019)	Pandemic (2020)	Total	p-value
Age, median (IQR)	51 (36-65)	54 (37-67)	52 (36-66)	0.025
Female, n (%)	972 (48.2)	531 (45.5)	1503 (47.2)	0.153
Male, n (%)	1045 (51.8)	636 (54.4)	1681 (52.8)	
Hospitalization, n (%)	284 (14.1)	299 (25.6)	583 (18.3)	<0.001
ICU admission, n (%)	28 (1.4)	34 (2.9)	62 (1.9)	0.003
Death in ED, n (%)	0 (0.0)	6 (0.5)	6 (0.2)	<0.001
IQR: Interquartile range, ICU: Intensive care unit, ED: Emergency department				

Discussion

In this study, despite the decrease in both general hospital and ED presentations during the COVID-19 pandemic, it was observed that the need for hospitalization and follow-up in the intensive care unit increased with the increase in recurrent ED presentations. In the management of the COVID-19 pandemic, the healthcare system attempted to provide the best medical care for those that contracted the disease while at the same time focusing on protecting other people that wanted to receive healthcare services without the risk of being infected (1). However, despite the need for acute medical assistance, there was a decrease in hospital presentation rates and patients were less willing to be treated in hospitals due to their fear of contracting the virus (7-9). The use of EDs as a primary option in the face of any health problem led to an increase in recurrent presentations. According to the literature, a global rate of 3% is acceptable for recurrent ED presentations (4). In the current study, although general hospital and ED presentations decreased in both pre-pandemic and pandemic periods, the rates of recurrent presentations were consistent with the global data.

In terms of service quality and efficiency, the number of patients and their characteristics are seen as a reflection of general in-hospital health services. In particular, in the last decade, the increase in the rate of recurrent presentations together with the increase in ED presentations has been the cause of overcrowded ED environments and has become a separate research topic for healthcare professionals (10). The clinical status of patients during their recurrent presentation is at a more critical level compared to their first presentation and is very important for both patient and physician safety. Similarly, in the current study, when the ED outcomes were evaluated, the need for inpatient follow-up in any clinic or intensive care unit was observed to double during the pandemic period, especially among the patients with recurrent presentations. The mean age of the patient group requiring inpatient follow-up and treatment during this period was also higher compared to the pre-pandemic period. Consistent with our findings, in a study conducted by Tangkulpanich et al. (11), recurrent ED presentations within 48 hours were examined, and it was observed that the likelihood of recurrent presentations increased as patient age increased. In addition, in our study, no mortality was observed during the pre-pandemic period, but six patients died during the pandemic period. Considering that the patients with mortality were all male and at an advanced age can be interpreted as an indication that these patients kept their medical support needs in the background due to the risk of contracting COVID-19. These findings are an indication of the absolute necessity of including recurrent presentations in the evaluation of the quality and efficiency of ED services.

When the patients with recurrent presentations were evaluated according to gender, it was determined that male gender was predominant both in the pandemic and pre-pandemic periods. However, in studies conducted in the pre-pandemic period in the literature, it was reported that female patients were more likely to revisit EDs (12,13). This discrepancy may be due to differences in the social characteristics, age, and existing chronic diseases.

Conclusion

In this study, we aimed to evaluate the effects of the current pandemic period on recurrent presentations by evaluating the number of patients and outcomes and to reveal how these data were affected as indicators of ED quality. The increase in the need for hospitalization and intensive care and mortality being observed in ED during the pandemic period demonstrate the negative effects of increased hospital density due to the pandemic on the effective operation of ED. The lack of similar studies published in the literature also shows that there is a need for many detailed studies to be conducted with larger populations in order to elucidate changes in recurrent patient presentations during the pandemic period.

The most important limitation of our study is that we did not separately evaluate patient complaints, examinations requested and their results, consultations made to other departments, and diagnoses among the patients with recurrent presentations. Therefore, we were not able to determine factors that could cause patients to revisit the hospital. Further comprehensive and detailed studies on this subject can be guiding.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Recep Tayyip Erdoğan University Faculty of Medicine Non-Invasive Clinical Research Ethics Committee (decision number: 2021/69, date: 08.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: M.A., Ö.B., Ö.Y., Design: M.A., Ö.B., M.Al., Data Collection or Processing: M.A., G.E., Analysis or Interpretation: M.A., G.E., Ö.Y., Literature Search: M.A., M.Al., Writing: M.A., Ö.B., G.E., M.Al.

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Original Article / Özgün Araştırma

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The Value of Atherogenic Index of Plasma in Estimating Coronary Artery Calcium Scores

Plazma Aterojenik İndeksinin Koroner Arter Kalsiyum Skorlarını Tahmin Etmedeki Değeri

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Abstract

Objective: Coronary calcium load is a strong indicator of the presence and severity of atherosclerotic plaques in the coronary arteries. The atherogenic index of plasma (AIP) has been established for the evaluation of plasma atherogenicity and is strongly associated with an increased cardiovascular risk. Herein, we aimed to explore the compatibility of the risk groups determined by the coronary artery calcium (CAC) score and the risk groups predicted by the AIP.

Materials and Methods: The records of 173 patients who underwent cardiac computed tomography for suspected coronary artery disease between January 2019 and January 2022 were analyzed. Patients were divided into five groups based on calculated CAC cut-off values that have been commonly used in the literature.

Results: Regarding, calculated AIP levels, patients with severe CAC had significantly higher levels of AIP compared to other groups ($p<0.001$). To determine the AIP cut-off value to predict severe CAC, the receiver operating characteristic curve was drawn and the best cut-off value was determined as 0.60 by using the Youden index, (area under the curve: 0.774, 95% confidence interval: 0.685-0.863, $p<0.001$). Above this threshold, CAC could be detected with a sensitivity of 75.8% and a specificity of 67.1%.

Conclusion: This study demonstrated that the AIP is an independent predictor of coronary calcification.

Keywords: Atherogenic index of plasma, coronary artery calcium score, computed tomography

Öz

Amaç: Koroner arter kalsiyum (KAK) yükü, koroner arterlerdeki aterosklerotik plakların varlığının ve ciddiyetinin güçlü bir göstergesidir. Plazmanın aterojenik indeksi (AIP), plazma aterojenitesinin değerlendirilmesi için oluşturulmuştur ve artmış kardiyovasküler risk ile güçlü bir şekilde ilişkilidir. Burada KAK skoruna göre belirlenen risk grupları ile AIP tarafından tahmin edilen risk gruplarının uyumluluğunu araştırmayı amaçladık.

Gereç ve Yöntemler: Ocak 2019 ile Ocak 2022 tarihleri arasında koroner arter hastalığı şüphesi nedeniyle kardiyak BT çekilen 173 hastanın kayıtları incelendi. Hastalar literatürde yaygın olarak kullanılan hesaplanan KAK kesim değerlerine göre beş gruba ayrıldı.

Bulgular: Hesaplanan AIP düzeylerine bakıldığında şiddetli KAK hastalarında diğer gruplarla karşılaştırıldığında anlamlı düzeyde daha yüksek AIP düzeyleri mevcuttu ($p<0,001$). Şiddetli KAK'yi öngörmek için AIP kesim değerini belirlemek amacıyla alıcı işletim karakteristiği eğrisi çizildi ve Youden indeksi kullanılarak en iyi kesim değeri 0,60 olarak belirlendi, (eğrinin altında kalan alan: 0,774, %95 güven aralığı: 0,685-0,863, $p<0,001$). Bu eşiğin üzerinde KAK %75,8 duyarlılık ve %67,1 özgüllükle tespit edilebildi.

Sonuç: Bu çalışma AIP'nin koroner kalsifikasyonun bağımsız bir belirleyicisi olduğunu gösterdi.

Anahtar Kelimeler: Plazmanın aterojenik indeksi, koroner arter kalsiyum skoru, bilgisayarlı tomografi

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Introduction

Calcium load strongly indicates of the presence and severity of atherosclerotic plaque in the coronary arteries (1-3). Previous reports have shown that calcium load not only provides prognostic information for describing patients at high risk of future cardiovascular events but also acts as a predictor of mortality over and above conventional cardiovascular risk factors (4-6). In this context, computed tomography (CT), a non-invasive tool for assessing the extent of coronary calcification, strongly predicts future cardiovascular events based on calculated coronary artery calcium (CAC) scores (7,8). However, CT is not suitable for detecting early calcifications, including microcalcifications and fragmented calcifications (9).

The atherogenic index of plasma (AIP) has been established to assess plasma atherogenicity and is explosively associated with the increased cardiovascular threat (10-12). It has been reported that this index is more effective than other atherogenic biomarkers or individual lipoprotein indices in distinguishing the high-risk population (13,14). On the other hand, no related research has investigated the contribution of AIP to the CAC score in determining the risk of coronary artery disease and its impact on the treatment decision, especially in cases where no consensus can be reached on the clinical approach. Because of these reasons, this study aimed to assess the harmoniousness of the risk groups determined by the CAC score and those predicted by the AIP.

Materials and Methods

Study Population

The study protocol was approved by the Clinical Research Ethics Committee of Necmettin Erbakan University Faculty of Medicine (decision no: 2022/3883, date: 01.07.2022). The study individuals were retrospectively identified from the medical archives of patients who underwent coronary CT for suspected coronary artery disease between January 2019 and January 2022. Demographic and clinical factors of the study individuals and the indication for cardiac CT imaging were analyzed retrospectively. Exclusion criteria were active infection, presence of malignancy, history of chronic inflammatory disease, liver failure, chronic renal disease (serum creatinine level ≥1.5 mg/dL), and documented coronary artery disease. Acute coronary syndrome patients were also excluded from the study. One hundred seventy-three study patients were enrolled. Informed consent form was taken from all study patients, and the study was approved by the committee following the ethical guidelines of the 1975 Declaration of Helsinki.

CAC Assessment

CAC imaging with high temporal resolution was performed via a 64-slice multi-detector CT scanner (Siemens Medical Solutions, Forchheim, Germany). Consecutive slices were acquired during a single breath hold from the tracheal bifurcation to the level of the diaphragm. According to this method, a lesion was defined as ≥3 consecutive pixels with a peak attenuation of at least 130 Hounsfield units (HU) and an area of ≥1 mm^2 (15). With its peak HU, each area of calcified plaque was measured for the left coronary and right coronary vessels and pooled to calculate the total CAC score using software (Syngo Multimodality Workplace Siemens, Siemens, Germany). Total CAC scores were defined as none (0), minimal (1-10), mild (11-100), moderate (101-400), or severe (≥400) based on cut-off values commonly used in the literature (15). All CAC scores were calculated by two radiologists who blinded to clinical data. Study participants were divided into five categories with similar numbers of patients based on their calculated total CAC score. The AIP was calculated with the formula AIP= log [triglyceride (TG)/ high-density lipoprotein (HDL-C)] (16).

Statistical Analysis

Continuous data are presented as mean ± standard deviation if normally distributed, or as median (25^{th}-75^{th} percentiles), if not normally distributed. Continuous variables were compared using Student's t-test or the Mann-Whitney U test. Categorical variables are expressed as numbers and percentages and were analyzed using the χ^2 test or Fisher's exact test. A multivariate Cox regression analysis was used to identify the risk factors for the estimation of CAC scores; hazard ratios and 95% confidence intervals (CIs) were calculated. All statistical analyses were conducted using SPSS software version 24.0 for Windows (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant during the study. The area under the receiver operating characteristic (ROC) curves (AUCs) was used to assess the predictive value of the AIP for the presence of severe coronary calcification. The Youden index was also used to determine the best cut-off value for the AIP to predict severe coronary calcification.

Results

From January 2019 to January 2022, of the 867 patients screened, a total of 173 patients met all selection criteria and were ultimately included in the study. The baseline demographic, electrocardiographic, echocardiographic, and laboratory characteristics of the patients are given in Table 1. There were no significant differences in electrocardiographic and echocardiographic characteristics between all groups. Regarding baseline laboratory values, all groups had similar laboratory characteristics ($p>0.05$). However, plasma neutrophil count, blood urea nitrogen (BUN), serum total cholesterol, serum TGs, and serum HbA1c were significantly higher in patients with severe CAC compared to other groups ($p<0.05$). Serum HDL levels were also significantly lower in patients with severe CAC compared to other groups ($p<0.05$). In terms of calculated AIP levels, patients with severe CAC had significantly higher AIP levels compared to other study groups ($p<0.001$).

To identify the prognostic indicators of severe CAC, several variables were included in the univariate Cox regression analysis. After removing the variables that did not affect the presence of severe CAC in the univariate analysis, multivariate Cox regression analysis was performed, which identified serum BUN level, serum HbA1c level, and AIP as independent predictors of severe CAC (Table 2). According to our data, AIP was the best predictor of CAC among the aforementioned parameters (p<0.001). To determine the AIP cut-off value for predicting severe CAC, the ROC curve was plotted and the best cut-off value was determined to be 0.60 with the Youden index (AUC: 0.774, 95% CI: 0.685-0.863,

Table 1. The demography, electrocardiography, echocardiography, and laboratory parameters of the patients according to the CAC scores

Parameters	CAC score: 0 (n=32)	CAC score: 1-10 (n=35)	CAC score: 11-100 (n=38)	CAC score: 101-400 (n=35)	CAC score ≥400 (n=33)	p-value
Age (years)	54.5 (39-78)	57 (32-80)	56 (33-81)	54 (36-88)	59 (39-81)	0.700
Sex: Male, n (%)	22 (68.8)	25 (71.4)	25 (65.8)	26 (74.3)	26 (78.8)	0.786
Smoking, n (%)	14 (43.8)	15 (42.9)	17 (44.7)	20 (57.1)	20 (60.6)	0.430
Electrocardiography parameters						
Heart rate (min)	76 (55-90)	76 (60-102)	77 (55-96)	77 (56-98)	82 (61-96)	0.263
PR interval (ms)	145 (120-200)	146 (120-176)	153 (110-180)	160 (110-200)	152 (110-190)	0.618
QRS duration (ms)	96 (80-110)	90 (80-110)	92 (80-128)	93 (80-120)	96 (80-127)	0.577
QTc interval (ms)	391 (350-442)	400 (335-455)	396 (340-450)	398 (328-446)	400 (340-465)	0.972
Echocardiography parameters						
LVEF (%)	62.0±4.9	61.2±5.4	60.4±6.2	59.9±6.2	60.3±6.6	0.599
LVEDD (mm)	4.5±0.3	4.6±0.3	4.6±0.4	4.7±0.4	4.6±0.3	0.972
LVESD (mm)	2.8±0.2	2.9±0.3	2.9±0.3	2.9±0.3	2.8±0.3	0.979
Laboratory parameters						
WBC (x10^3/μL)	7.3 (4.1-15.4)	7.4 (4.8-12.0)	7.7 (4.5-15.5)	7.7 (5.2-18.3)	8.6 (4.4-13.9)	0.076*
Neutrophils (x10^3/μL)	4.2 (1.8-12.3)	4.1 (1.7-8.8)	4.3 (2.1-12.3)	4.2 (2.9-16.1)	4.9 (2.9-10.4)	0.029*
Lymphocytes (x10^3/μL)	2.1 (1.1-3.8)	2.2 (1.2-4.3)	2.3 (1.5-3.7)	2.5 (0.9-4.0)	2.6 (0.3-3.6)	0.486
Hemoglobin (g/dL)	14.1 (11.3-16.9)	14.4 (11.1-17.0)	15.2 (10.5-17.4)	15.0 (11.5-17.5)	14.8 (11.4-16.8)	0.095
Platelets (x10^3/μL)	221 (132-408)	254 (179-379)	251 (133-424)	273 (127-436)	275 (129-393)	0.404
Creatinine (mg/dL)	0.82 (0.59-1.14)	0.86 (0.56-1.23)	0.90 (0.52-1.12)	0.94 (0.51-1.20)	0.92 (0.62-1.20)	0.070
GFR (mL/min)	87 (61-120)	92 (60-121)	91 (68-125)	90 (61-132)	88 (64-131)	0.512
BUN (mg/dL)	28 (17-44)	25 (12-48)	28 (16-42)	28 (21-47)	32 (21-49)	0.013*
HbA1c (%)	5.5 (4.6-7.7)	5.8 (4.8-6.6)	6.0 (4.7-9.5)	6.0 (4.7-9.4)	6.1 (4.7-9.7)	0.001*
ALT (IU/mL)	21 (8-44)	21 (7-45)	20 (9-45)	23 (9-44)	24 (11-48)	0.889
Total cholesterol (mg/dL)	169 (123-238)	200 (95-271)	205 (70-250)	211 (99-302)	197 (133-325)	0.002*
LDL (mg/dL)	101 (43-167)	118 (36-182)	122 (21-175)	124 (28-212)	109 (61-218)	0.070
HDL (mg/dL)	50 (31-80)	46 (34-86)	42 (25-66)	40 (25-70)	38 (27-61)	<0.001*
Triglycerides (mg/dL)	89 (53-188)	126 (55-329)	174 (91-309)	212 (94-392)	231 (75-646)	<0.001*
AIP	0.26 (0.02-0.75)	0.38 (0.07-0.74)	0.57 (0.21-0.98)	0.75 (0.30-1.10)	0.81 (0.23-1.50)	<0.001*

CAC: Coronary artery calcium, PR: Prevalence ratio, LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastolic distance, LVESD: Left ventricular end-systolic dimension, WBC: White blood cell, GFR: Glomerular filtration rate, BUN: Blood urea nitrogen, ALT: Alanine transferase, LDL: Low-density protein, HDL: High-density lipoprotein, AIP: Atherogenic index of plasma

Table 2. Regression analyses for the prediction of CAC score

Parameters	Univariate			Multivariate		
	B±SE	95% CI	p-value	B ± SE	95% CI	p-value
WBC (x10³/μL)	0.118±0.046	0.026-0.209	0.012*	-0.039±0.101	(-0.238)-0.160	0.701
Neutrophils (x10³/μL)	0.114±0.052	0.012-0.216	0.029*	0.037±0.043	(-0.048)-0.122	0.393
Hemoglobin (g/dL)	0.106±0.064	(-0.020)-0.231	0.098	-	-	-
Creatinine (mg/dL)	1.720±0.635	0.466-2.974	0.007*	0.338±0.510	(-0.670)-1.346	0.509
BUN (mg/dL)	0.036±0.014	0.009-0.062	0.009*	0.027±0.010	0.007-0.047	0.010*
HbA1c (%)	0.471±0.098	0.277-0.664	<0.001*	0.272±0.085	0.105-0.439	0.002*
Total cholesterol (mg/dL)	0.007±0.002	0.002-0.012	0.004*	-0.004±0.004	(-0.012)-0.004	0.316
LDL (mg/dL)	0.006±0.003	0.000-0.012	0.037*	0.003±0.002	(-0.002)-0.007	0.239
HDL (mg/dL)	-0.054±0.009	(-0.071)-(-0.037)	<0.001*	0.004±0.012	(-0.020)-0.029	0.738
Triglycerides (mg/dL)	0.008±0.001	0.006-0.010	<0.001*	0.000±0.002	(-0.004)-0.004	0.816
AIP	3.273±0.283	2.715-3.830	<0.001*	3.061±0.289	2.490-3.632	<0.001*

CAC: Coronary artery calcium, CI: Confidence interval, WBC: White blood cell, BUN: Blood urea nitrogen, LDL: Low-density protein, HDL: High-density lipoprotein, AIP: Atherogenic index of plasma

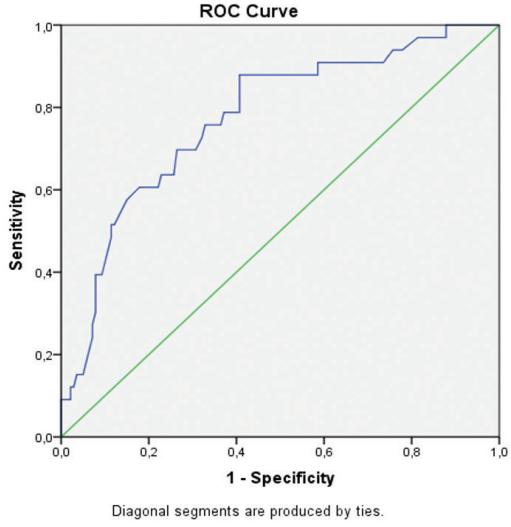

Figure 1. The ROC curve of AIP for predicting CAC score ≥400
AIP ≥0.60 sensitivity 75.8%, specificity 67.1%
AUC: 0.774 (95% CI: 0.685-0.863), p<0.001
ROC: Receiver operating characteristics, AIP: Atherogenic index of plasma, CAC: Coronary artery calcium, AUC: Areas under the curve, CI: Confidence interval

p<0.001; Figure 1). Above this threshold, CAC was detected with a sensitivity 75.8% and a specificity 67.1%.

Discussion

The key finding of this study is that AIP is may be a useful and valuable indicator of the extent of coronary calcification in patients with uncertain and suspected coronary artery disease. As we know in the literature, this is the first study to demonstrate the strong relationship between AIP and the severity of coronary calcification in patients with suspected coronary artery disease.

Primary prevention of CVD includes low-risk strategies such as behavioral and lifestyle management, as well as treatment modalities for optimal control of comorbidities (1). Furthermore, the identification of individuals who would benefit from cardiovascular treatment could place an enormous burden on the healthcare system, and it remains a challenge for physicians to assess the appropriate patients with the most appropriate diagnostic approach to classify cardiovascular risk. Therefore, various risk stratification tools have been developed to identify study patients who are not only at high risk for future cardiovascular events but also prefer invasive and non-invasive cardiovascular treatment. In this context, CAC imaging has been developed as a quantitative measure of coronary atherosclerotic burden and a predictor of future cardiovascular events in patients with uncertain and suspected coronary artery disease (17,18). Based on the available data, when applied to selected individuals, this diagnostic approach has a high discriminatory ability for the degree of coronary artery disease and may prevent further examination of coronary artery disease. In addition, this imaging modality is useful in assessing myocardial scar and the size of the ventricles and ascending aorta (19). However, the predictive value of CAC estimation for detecting coronary plaque instability remains controversial (9). Furthermore, lower CAC values are not sufficient to exclude an increased risk of future cardiovascular events, especially in individuals with modifiable cardiovascular risk factors such as diabetes mellitus, smoking, or a family history of premature cardiovascular death (20). Therefore, the American Heart

Association guidelines for cholesterol screening do not recommend the diagnostic use of CAC imaging in people with these risk factors (21). Therefore, novel non-invasive diagnostic tests are urgently needed to determine the pre-test probability of uncertain coronary artery disease and to accurately stratify people with uncertain coronary artery disease.

In our study, we used the most appropriate atherosclerotic index to examine the presence and degree of coronary artery disease in patients undergoing cardiac CT for suspected coronary artery disease. In addition, to observe the relationship between CAC score and AIP, we divided patients into subgroups according to their current CAC score. According to our data, when patients were divided into subgroups with similar numbers, significantly higher AIP levels were found in patients with high CAC scores.

As there is a direct link between altered lipid metabolism and the onset and development of coronary heart disease, the logarithm of the molar ratio of TG to HDL-C is consistent with an elevated risk of coronary heart disease (22,23). Furthermore, this relationship has been confirmed by several studies in different atherosclerotic conditions such as obesity, hypertension, DM, insulin resistance, and metabolic syndrome (24-25). Therefore, AIP stands out as a potential biomarker for research into the presence and severity of coronary artery disease. However, any other studies have not investigated the association between AIP and an increased risk of coronary heart disease, especially in people without a known history of coronary heart disease. In our study, we used a well-known CT imaging parameter to confirm the presence of atherosclerosis and observed a significant correlation between AIP and the calculated total CAC score. According to our study, the higher the CAC score, the higher the AIP value. After adjustment for variables affecting the presence and degree of coronary artery disease, multivariate regression analysis determined that AIP was still an independent risk factor for severe CAC. Based on these results, we suggest that high AIP can be considered a quantitative measure of coronary atherosclerotic burden and an indicator of future cardiovascular scenes in patients with uncertain coronary artery disease.

There are some limitations of our study. First, it is a retrospective, single-center study with a limited number of patients. Second, due to the lack of continuous measurement of blood tests in this study, AIP levels were measured at a single point in time, and the fluctuation of AIP levels was not taken into account. Follow-up monitoring could be provide extra predictive value. Thirdly, we did not compare AIP measurements with other hematological and biochemical markers.

Conclusion

The current study revealed that the AIP is an independent predictor of coronary calcification. This index is a simple, inexpensive, and non-invasive prognostic tool that can be used for cardiovascular risk stratification.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Necmettin Erbakan University Faculty of Medicine (decision no: 2022/3883, date: 01.07.2022).

Informed Consent: Informed consent form was taken from all study patients, and the study was approved by the committee following the ethical guidelines of the 1975 Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.L.S., A.İ., C.K., Concept: A.L.S., Design: A.T.Ş., Data Collection or Processing: A.T.Ş., C.K., P.D.Y., Analysis or Interpretation: N.A., A.İ., Literature Search: M.D., A.İ., Writing: A.L.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article / Özgün Araştırma

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Comparison of Surgical Outcomes in External Dacryocystorhinostomy: Conventional Approach versus Viscoelastic-assisted Approach

Eksternal Dakriyosistorinostomide Cerrahi Sonuçların Karşılaştırılması: Konvansiyonel Yaklaşıma Karşı Viskoelastik Destekli Yaklaşım

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Abstract

Objective: To compare the surgical success rate between viscoelastic-facilitated external dacryocystorhinostomy (DCR) surgery and conventional external DCR surgery in patients with acquired nasolacrimal duct obstruction.

Materials and Methods: In this retrospective, comparative cohort study, data of patients who underwent external DCR surgery and silicone tube intubation between 2017 and 2023 were evaluated. Among the 99 cases with no prior surgical history, 46 cases were allocated to the viscoelastic group (viscoelastic substance was used to fill the lacrimal sac just before creating the mucosal flaps), while 53 cases were allocated to the conventional group. All surgeries were performed by the same surgeon. Surgical success was defined as the presence of an open lacrimal drainage system confirmed by a lacrimal irrigation test and/or relief of epiphora.

Results: There were no significant differences observed between the groups with regards to age, gender, DCR tube extubation time, and side of the surgery (right/left lacrimal sac) (p>0.05). The mean follow-up was 27.8±20.9 (6-66) months in the viscoelastic group and 22.9±20.2 (6-64) months in the conventional group (p=0.35). Two cases in the viscoelastic group and four cases in the conventional group experienced recurrence during the follow-up period. Surgical success rates were calculated as 95.7% and 92.5% for the viscoelastic group and the conventional group, respectively (p=0.68).

Conclusion: Viscoelastic-assisted external DCR surgery is as successful as conventional external DCR surgery. We are particularly of the opinion that this approach would enhance surgical success, especially in cases where the lacrimal sac is small and fibrotic.

Keywords: Dacryocystorhinostomy, dacryocystitis, epiphora, nasolacrimal duct, viscoelastic substance

Öz

Amaç: Çalışmanın amacı edinilmiş nazolakrimal kanal tıkanıklığı olan olgularda, viskoelastik ile kolaylaştırılmış eksternal dakriyosistorinostomi (DSR) cerrahisi ile konvansiyonel eksternal DSR cerrahisi başarı oranlarını karşılaştırmaktır.

Gereç ve Yöntemler: Bu retrospektif, karşılaştırmalı kohort çalışmasında 2017-2023 yılları arasında eksternal DSR cerrahisi ve silikon tüp entübasyonu uygulanın hastaların verileri değerlendirildi. Daha önce cerrahi geçirmemiş toplam 99 olgudan 46'sı viskoelastik grubuna (mukozal flepler oluşturulmadan hemen önce, lakrimal kese, viskolelastik madde ile dolduruldu), 53'ü konvansiyonal gruba dahil edildi. Bütün cerrahiler aynı hekim tarafından gerçekleştirildi. Lavaj ile nazolakrimal kanalın açık olması ve/veya hastanın epifora şikayetlerinin geçmesi cerrahi başarı olarak kabul edildi.

Bulgular: Gruplar arasında yaş, cinsiyet, silikon DSR tüpünün alınma zamanı ve cerrahi taraf açısından anlamlı fark yoktu (p>0,05). Ortalama izlem süresi viskoelastik grubunda 27,8±20,9 (6-66) ay, konvansiyonel grupta 22,9±20,2 (6-64) ay idi (p=0,35). Viskoelastik grubunda 2 hastada, konvansiyonel grupta 4 hastada nüks gelişti. Cerrahi başarı oranları viskoelastik grup ve konvansiyonel grup için sırasıyla %95,7 ve %92,5 olarak hesaplandı (p=0,68).

Sonuç: Viskoelastik madde yardımı ile kolaylaştırılmış eksternal DSR cerrahisi en az standart eksternal DSR cerrahisi kadar başarılıdır. Özellikle lakrimal kesenin küçük ve fibrotik olduğu olgularda bu yöntemin cerrahi başarıyı artırabileceği kanaatindeyiz.

Anahtar Kelimeler: Dakriyosistorinostomi, dakriyosistit, epifora, nazolakrimal kanal, viskoelastik madde

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Introduction

External dacryocystorhinostomy (DCR) and/or silicone tube intubation is currently the most frequently employed surgical method for the treatment of acquired nasolacrimal duct obstruction or stenosis. It was first described by Toti (1) and further developed by Dupuy-Dutemps and Bourguet (2,3). While external DCR is a surgical technique known for its high success rates, achieving the desired outcomes may not always be guaranteed, even in the hands of experienced surgeons. Therefore, in pursuit of improved surgical outcomes, there is an ongoing endeavor to explore innovative techniques or make modifications to existing approaches.

Ophthalmic viscosurgical devices (OVDs) were introduced for the purpose of creating and maintaining adequate intraocular space during phacoemulsification surgery and intraocular lens implantation (4). As various OVDs have evolved, their applications have expanded beyond maintaining intraocular space during intraocular surgery. These devices are now utilized for additional purposes, including safeguarding the corneal endothelium, enlarging and stabilizing pupil size, and addressing specific challenges such as small pupils or intraoperative floppy iris syndrome.

In addition to their established role in intraocular surgery, to our knowledge, this is the first report of the use of OVDs to facilitate the preparation of lacrimal sac flaps in DCR surgery. In this framework, our objective was to present the outcomes of viscoelastic-facilitated external DCR surgery compared to conventional external DCR surgery in patients with acquired nasolacrimal duct obstruction.

Materials and Methods

The research protocol of this retrospective comparative study was reviewed and approved by the Ethical Committee and Review Board of İzmir Bakırçay University, ensuring compliance with the ethical guidelines stated in the Declaration of Helsinki (decision number: 1072, date: 07.06.2023). The retrospective evaluation involved the medical records of patients who underwent external DCR surgery and silicone tube intubation at the Department of Ophthalmology, İzmir Bakırçay University Çiğli Training and Research Hospital, between January 2017 and July 2023. The cases in which a viscoelastic substance was used to fill the lacrimal sac and to create mucosal flaps during the surgery were included in the viscoelastic study group. The remaining cases were assigned to the conventional study group. The nasolacrimal duct obstruction diagnosis was confirmed through the performance of the lacrimal washout test. All surgical procedures were conducted by the same surgeon under general anesthesia. Surgical success was determined based on the criteria of an unobstructed lacrimal drainage system, as evidenced by a lacrimal irrigation test and/or relief of epiphora. The exclusion criteria for this study encompassed patients under the age of 15, a postoperative follow-up period of less than 6 months, previous lacrimal surgery with a history of failed DCR, the presence of canalicular or common canalicular obstruction, bony deformities, punctal stenosis, evident lid laxity, entropion, and ectropion.

Surgical Procedure

After placing an adrenaline-soaked tamponade in the nasal cavity for hemostasis control, a 15-20 mm long incision was made on the skin and subcutaneous tissue, 10 mm away from the medial canthus. While preserving the angular vein, blunt dissection was made. The periosteum was exposed and incised parallel to the anterior lacrimal crest. Using the periosteal elevator, the periosteum was gently elevated from the underlying bone, and the lacrimal sac was positioned laterally, then, the lacrimal fossa was exposed. A 15x15 mm nasal osteotomy was created over the lacrimal fossa, using a Kerrison bone punch. In the conventional study group, an H-shaped full-thickness lacrimal sac mucosal incision was then made to the medial wall of the lacrimal sac to create anterior and posterior lacrimal mucosal flaps. On the other hand, in the viscoelastic study group, the cannula of a cohesive ophthalmic viscoelastic substance [DisCoVisc (Alcon Laboratories, Inc.) or Healon GV (Johnson & Johnson surgical vision, Inc.) was used in this study] was inserted into the inferior punctum. The viscoelastic substance was injected through the inferior canaliculus until it was observed coming from the superior punctum and the lacrimal sac was distended before its incisions (Image 1). Then, lacrimal sac anterior and posterior mucosal flaps were created with an H-shaped full-thickness lacrimal sac mucosal incision same as the conventional study group. The remaining surgical steps were identical in both study groups. After removing intranasal tamponade, nasal anterior and posterior mucosal flaps were prepared and posterior

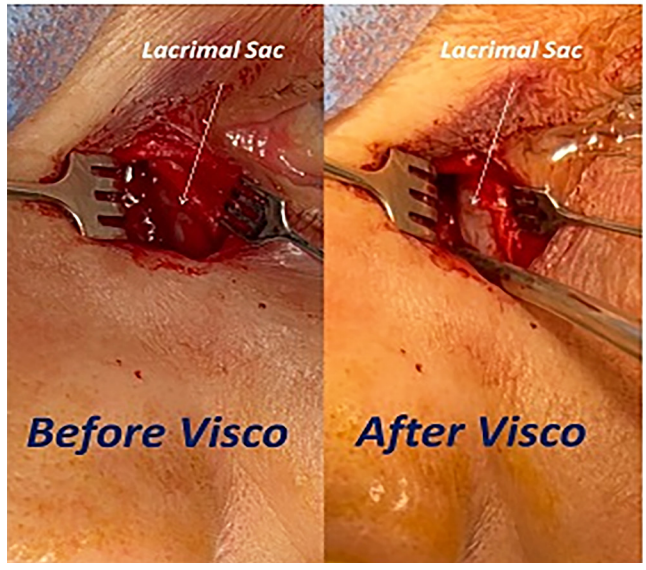

Image 1. The appearance of the lacrimal sac before and after filling with viscoelastic substance. After injection into the lacrimal sac, viscoelastic material leads to noticeable distention of the sac

flaps of the nasal and the sac mucosa were sutured with 6-0 surgical vicryl suture. A bicanalicular silicone DCR tube intubation was performed and then anterior mucosal flap anastomosis was made using a 6-0 vicryl suture. After the DCR silicone tube was secured in the nasal cavity, the periosteum and subcutaneous tissues were meticulously sutured using 6-0 vicryl, and the skin was subsequently closed with a 5-0 prolene suture.

Statistical Analysis

Before conducting statistical analysis, the assumption of normality for numerical variables was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics were presented as mean ± standard deviation (minimum-maximum) for continuous variables and frequency (%) for categorical variables. To compare continuous variables between the two independent groups, it was conducted Mann-Whitney U test for non-parametric data and the Independent Samples t-test for parametric data. The chi-square test and Fisher's exact test were employed to assess the association between categorical variables. The significance level was set at $p<0.05$ to determine the statistical significance.

Results

A total of 99 out of 105 cases who underwent external DCR surgery and silicone tube intubation over a period of approximately 5 years were included in this study. The demographic properties of these cases are given in Table 1. There were 46 cases in the viscoelastic group and 53 cases in the conventional group. No statistically significant differences were found between the groups in terms of age, gender, side of the surgery, DCR silicone tube extubation time, and postoperative follow-up duration (Table 1). There were no reported complications during the surgical procedures. At the final examination, recurrence was observed in 2 patients from the viscoelastic group and 4 patients from the conventional group. The calculated surgical success rates were 95.7% for the viscoelastic group and 92.5% for the conventional group, with no statistically significant difference observed between the two groups (p=0.68).

Discussion

Although endonasal DCR has gained popularity in recent years due to its advantages, including an absence of cutaneous scar and a shorter operation time, comparative studies have shown that its outcomes may not match those achieved with the traditional external approach, highlighting the external DCR surgery remains the established and widely accepted treatment modality for acquired nasolacrimal duct obstruction (5). In this retrospective comparative cohort study, we described a different approach to the lacrimal sac in external DCR surgery and compared the outcomes with the conventional approach. To the extent of our knowledge, this study represents the first investigation in the literature to examine the potential superiority of using a viscoelastic substance during the procedure compared to the conventional technique. The findings of the present study demonstrated a slightly elevated rate of success in the viscoelastic group as an effective technique for the treatment of acquired nasolacrimal duct obstruction, with 95.7% of patients achieving a successful resolution of symptoms at the mean 28 months follow-up period. However, the observed variation in success rates between the groups did not reach statistical significance.

In the literature, success rates of external DCR range from 73% to 100% (6). The success rates of DCR can be influenced by various factors, such as the insufficient bony aperture between the nasal cavity and the lacrimal sac, the presence of membranous occlusion due to scarring at the rhinostomy site, intranasal adhesions, scar tissue involving the middle turbinate and nasal septum, canalicular stenosis, and multiple surgeries (7). In other words, the development of excessive granulation tissue, and fibrotic scarring during the wound healing process can lead to stenosis of the common canaliculus or closure of the nasal osteotomy, ultimately resulting in the failure of DCR surgery (8). Although recent studies have described the use of only anterior flaps, referred to as the single-flap technique, and yield comparable results to conventional double-flap surgery, a review study highlighted that preserving anterior and posterior flaps of the nasal mucosa and lacrimal sac and performing double-flap technique can contribute to reducing granulation tissue formation and result in better

Table 1. Demographic properties and surgical success rates of the groups

	Viscoelastic group n=46	Conventional group n=53	p-value
Age (years)	60.7±11.9 (23-80)	59.6±12.4 (34-77)	0.84*
Gender (female/male)	34 (73.9%)/12 (26.1%)	44 (83.0%)/9 (17.0%)	0.33†
Side (right/left)	21 (45.7%)/25 (54.3%)	23 (43.4%)/30 (56.6%)	0.84†
DCR silicone tube extubation (months)	3.5±1.7 (2-6)	3.9±1.7 (2-6)	0.14*
Follow-up (months)	27.8±20.9 (6-66)	22.9±20.2 (6-64)	0.35*
Surgical success	44/46 (95.7%)	49/53 (92.5%)	0.68‡

n: number of cases, *Mann-Withney U test, †Chi-square test, ‡Fisher's exact test

ostium opening when conducting DCR procedures as a routine practice (9,10). Therefore, lacrimal sac manipulation and preparation of lacrimal flaps play a pivotal role in the overall success of DCR surgery. However, it is often regarded as one of the most critical and intricate steps in the procedure. Particularly challenging is the management of a fibrosed or anatomically altered lacrimal sac, as H-shaped incisional manipulations to create lacrimal mucosal flaps in such cases may result in iatrogenic damage not only to the mucosa but also the common canaliculus, contributing to poorer surgical outcomes. Additionally, it is well known that minimizing mucosal trauma plays a crucial role in minimizing wound contraction and scar formation (10,11). Some authors suggested that this is also the case in DCR, therefore, the atraumatic manipulations and careful apposition of the nasal mucosa and lacrimal flaps during surgery facilitate the process of primary intention healing, leading to a decreased incidence of granulation tissue formation (12).

In the current study, a more secure and controlled opening of the lacrimal sac is achieved by using a cohesive viscoelastic substance. The concept of filling the lacrimal sac with a viscoelastic substance was initially introduced in the literature by Baddeley et al. (13). However, their study focused on a patient with Wegener's granulomatosis undergoing dacryocystectomy. They described a technique involving canalicular clamping and the injection of a viscoelastic substance into the lacrimal sac aiming to enhance dissection ease during the dacryocystectomy procedure. Based on this study reported by Baddeley et al. (13), we have considered that viscoelastic substances can be utilized not only in dacryocystectomy surgery but also in DCR surgery, during the stage of lacrimal sac incision and flaps creation, which is known as the most challenging and critical step of the surgery. Through the application of a cohesive viscoelastic substance, the medial wall of the lacrimal sac is gently elevated, resulting in enhanced visual clarity during the specific phase of making incisions of the medial wall in the surgical procedure. Simultaneously, it creates a separation between the medial and lateral walls of the lacrimal sac, facilitating a safer entry into the lacrimal sac, reducing the risk of canalicular communis damage, and minimizing potential complications. The distention of the lacrimal sac and the displacement of the medial wall away from the lateral wall where the opening of common canaliculus is located, are particularly crucial in cases of small and fibrotic lacrimal sacs with lower surgical success rates.

The present study has several strengths that contribute to its robustness and reliability. This study's primary strength lies in the implementation and evaluation of a modified technique for external DCR surgery in a considerable number of patients conducted at a single center under the expertise of a single surgeon. The study also demonstrates a noteworthy strength in its extensive mean follow-up period of approximately 2 years across the study cohorts, providing valuable insights into the long-term outcomes of the intervention. On the contrary, there are certain limitations that should be taken into consideration when interpreting the findings of this study. A significant drawback of this study is its retrospective design, which may introduce biases and limitations in data collection and analysis. Because of the lack of data about intraoperative measurements of lacrimal sac sizes, we were not able to evaluate the patients with fibrotic or small lacrimal sacs, which is the other limitation of this study. Therefore, randomized, controlled studies that include the evaluation of these patients are needed to further investigate the findings.

Conclusion

In conclusion, this study demonstrated the safety and comparable efficacy of the viscoelastic-assisted approach in external DCR surgery when compared to conventional DCR surgery in adult patients diagnosed with acquired nasolacrimal duct obstruction. We believe that this modified approach, incorporating the use of a cohesive viscoelastic substance can enhance the safe opening of the lacrimal sac during the surgery, particularly, in cases with smaller or fibrotic lacrimal sacs.

Ethics

Ethics Committee Approval: The research protocol of this retrospective comparative study was reviewed and approved by the Ethical Committee and Review Board of İzmir Bakırçay University (decision number: 1072, date: 07.06.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Üstündağ H, Mertoğlu C, Huyut MT. Oxyhemoglobin Dissociation Curve in COVID-19 Patients. Meandros Med Dent J 2023;24(1):58-64.

The mistake has been made inadvertently by the authors.

- **The sentences under the heading Abstract and Öz on page 58 have been changed.**

- Incorrect

Results: It was concluded that patients with COVID-19 and other respiratory distress patients had a slight right-leaning trend in the ODC compared with the standard curve. The P50 value of the ICU group was higher than the other groups (mean: 30.74 mmHg, n=131, p=0.047). While the percentage of oxyhemoglobin (mean: 65.44% vs 69.81%, p=0.015), the amount of glucose (mean: 163.39 mg/dL vs 195.36 mg/dL, p=0.002) and pH (median: 7.38 vs 7.41, p=0.007) in the non-ICU group was higher compared with the control group, the carboxyhemoglobin percentage (mean: 1.66% vs 1.13%, **p=0.000**), PCO_2 (42.02 mmHg vs 39.44 mmHg, p=0.015), potassium (mean: 4.33 mmol/L vs 4.04, p=0.026), and sodium (mean: 138.10 mmol/L vs 135.80 mmol/L, **p=0.000**) were lower. The methemoglobin percentage of the ICU group was lower (**p=0.000**) than the other groups.

Bulgular: COVID-19 tanılı ve diğer solunum sıkıntılı hastaların ODC'lerinin standart eğriye göre hafif sağa eğilim gösterdiği belirlendi. YBÜ grubunun P50 değeri, diğer gruplara kıyasla daha yüksekti (ortalama: 30,74 mmHg, n=131, p=0,047). Kontrole kıyasla non-YBÜ grubunun; oksihemoglobin yüzdesi (ortalama: %65,44 vs %69,81, p=0,015), PO_2'ı (46,98 mmHg vs 48,98 mmHg, p=0,001), glikoz miktarı (ortalama: 163,39 mg/dL vs 195,36 mg/dL, p=0,002) ve pH'sı (medyan: 7,38 vs 7,41, p=0,007) daha yüksek iken karboksihemoglobin yüzdesi (ortalama: %1,66 vs %1,13, **p=0,000**), PCO_2'ı (42,02 mmHg vs 39,44 mmHg, p=0,015), potasyum (ortalama: 4,33 mmol/L vs 4,04, p=0,026) ve sodyum (ortalama: 138,10 mmol/L vs 135,80 mmol/L, **p=0,000**) seviyesi daha düşüktü. YBÜ grubunun methemoglobin yüzdesi ise diğer gruplara kıyasla daha düşüktü (**p=0,000**).

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- **A sentence has been changed under the title of Statistical Analysis on page 59, 11th line.**

- Incorrect

Tukey and Dunnett post-hoc tests determined significant changes' sources.

- Corrected

Tukey HSD or Games-Howell post-hoc tests were employed to assess differences between groups following one-way ANOVA analysis, while Dunn's post-hoc test was utilized to assess differences between groups after Kruskal-Wallis analysis.

- **The p=0.000 values in the p-values column in Table 1 on page 60 of the related article have been changed to p=0.001.**

- Incorrect

Table 1. Summary of results from patients with ICU COVID-19, non-ICU COVID-19 and control group without COVID-19																
	Non-ICU					ICU					Control					p-value
Sex																
Male N (%)	122 (57.5)					80 (61.1)					209 (60.9)					0.699
Female N (%)	90 (42.5)					51 (38.9)					134 (39.1)					
Parametreler	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Mean**	**Median**	**SD**	**Min.**	**Max.**	**Mean**	**Median**	**SD**	**Min.**	**Max.**	
Age	68.79*	71.00	14.47	20.00	96.00	71.51*	73.00	13.57	20.00	96.00	62.31#	66.00	20.07	19.00	102.00	**0.000**
P50 (mmHg)	29.25#	28.79	3.71	21.28	53.74	30.74*	29.66	5.86	21.74	74.39	29.38*#	28.52	6.67	20.65	110.98	0.047
Bicarbonate plasma (mEq/L)	24.18	24.25	4.19	10.30	37.70	24.48	23.80	5.84	11.60	51.00	23.66	23.90	4.42	5.30	42.00	0.252
Bilirubin (mg/dL)	1.60	1.45	1.06	0.00	8.00	2.43	1.50	4.04	0.00	33.00	1.57	1.50	0.93	0.10	7.00	0.838
Deoxyhemoglobin (%)	27.67	21.40	20.73	1.20	92.00	28.62	25.70	22.63	0.50	83.20	31.51	28.30	20.63	0.70	94.30	0.107
Glucoce (mg/dL)	195.36*	147.50	123.35	40.00	695.00	185.44	158.00*#	104.38	64.00	879.00	163.39#	131.00	96.39	55.00	743.00	0.002
HCO_3 (mEq/L)	24.46	24.35	3.92	15.50	33.60	23.84	25.05	6.32	7.40	43.50	24.00	23.90	3.81	13.20	38.70	0.771
Hematocrit (%)	42.48	41.95	12.41	0.90	82.60	40.35	40.40	11.78	5.50	73.90	42.69	43.00	10.25	10.10	78.60	0.118
Hemoglobin (g/dL)	13.85	13.70	4.10	0.01	27.20	13.06	12.90	3.91	4.00	24.10	13.94	14.10	3.40	3.10	25.70	0.086
Carboxyhemoglobin (%)	1.13#	1.00	0.61	-0.30	4.80	1.02#	1.00	0.52	-0.30	2.90	1.66*	1.30	1.45	-0.40	11.40	**0.000**
Chlorine (mmol/L)	106.26	106.00	6.85	74.00	136.00	107.35	107.00	9.65	86.00	145.00	106.09	106.00	8.58	2.60	142.00	0.367
Lactate (mmol/L)	2.09	1.80	1.21	0.10	6.90	2.23	1.80	1.52	0.50	9.30	2.07	1.70	1.35	0.00	13.70	0.506
Methemoglobin (%)	1.36*	1.30	.45	-1.10	3.30	1.20#	1.20	0.49	0.10	3.20	1.42*	1.40	0.44	-1.40	4.60	**0.000**
Oxyhemoglobin (%)	69.81*	75.70	20.60	5.70	96.50	69.20#*	72.15	22.54	15.40	96.80	65.44#	68.10	20.52	4.00	97.10	0.015
Oxygen saturation (%)	71.73	78.20	21.16	5.80	98.80	70.76	73.75	23.06	15.60	99.50	67.53	70.90	21.15	4.10	99.30	0.076
Osmalarite (mOsmol/L)	283.36	283.60	11.61	233.50	340.90	286.14	283.65	18.28	243.20	353.50	285.24	285.65	11.70	237.60	359.30	0.147
pH (7.35-7.45)	7.407*	7.415	0.079	7.019	7.557	7.390#*	7.408	0.101	7.047	7.590	7.384#	7.383	0.080	6.819	7.649	0.007
Potassium (mmol/L)	4.04#	3.90	1.37	2.30	16.80	4.14#*	4.00	0.86	2.40	7.00	4.33*	4.10	1.55	2.40	20.10	0.026
Sodium (mmol/L)	135.80#	136.00	5.92	111.00	164.00	137.61#*	137.00	8.11	117.00	171.00	138.10*	139.00	5.51	113.00	163.00	**0.000**
Standard base (±3 mmol/L)	0.12	0.25	5.10	-17.50	18.70	0.17	0.20	6.62	-18.80	22.80	0.03	0.30	5.71	-24.50	36.00	0.970
Total O_2 (mEq/L)	13.80#	13.80	5.19	2.30	30.10	12.47*	12.10	5.40	2.70	25.90	12.71#*	12.80	4.98	0.90	30.50	0.033
pCO_2 (mmHg)	39.44*	39.00	9.78	12.20	113.00	41.78#*	39.70	12.92	12.70	101.00	42.02#	41.90	9.79	5.40	89.30	0.015
pO_2 (mmHg)	48.98#*	44.05	24.26	11.00	177.00	56.86#	45.80	36.30	16.00	295.00	46.98*	40.00	31.08	5.70	281.00	0.001
Ionized calcium (mg/dL)	1.15*	1.16	0.12	0.58	1.86	1.10#	1.10	0.10	0.82	1.47	1.15*	1.15	0.12	0.69	1.96	**0.000**

The values in Table 1 are presented as mean and standard deviation (SD). Differences between groups with the same symbol were not statistically significant, while differences between groups with different symbols were found to be significant at a p-value of less than 0.05. ICU: Intensive care unit, COVID-19: Coronavirus disease-2019, SD: Standard deviation, min-max: Minimum-maximum

- Correct

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- **The "p=0.000" values on lines 19, 22, and 23 under the results section on page 61 have been changed to "p<0.001".**

- Incorrect

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Kind regards,

Meandros Medical and Dental Journal Editorial Board