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Original Article / Özgün Araştırma

Inherited Rare Factor Deficiencies: Single-centre Experience

Kalıtsal Nadir Faktör Eksiklikleri: Tek Merkez Deneyimi

Başak Koç, Bülent Zülfikar

İstanbul University Institute of Oncology, Department of Pediatric Hematology and Oncology, İstanbul, Turkey

Abstract

Objective: Bleeding is one of the most important problems in humans. Absence, deficiency or dysfunctions of protein factors in the coagulation system can cause prolonged bleeding, morbidity or mortality. Although factor VIII, factor IX and von Willebrand factor deficiencies are the most common, deficiencies in all other factors exist, called rare factor deficiencies. This study aimed to present the clinical presentations, laboratory findings, treatments, and surgical interventions in patients with rare factor deficiencies other than factor VII followed up in our clinic.
Materials and Methods: Patients who were diagnosed with rare factor deficiency other than factor VII in the department of pediatric hematology and oncology between July 1997 and June 2020 were included in this study. Patients' demographic characteristics, clinical presentations, family history, prothrombin time, activated partial thromboplastin time and factor levels, treatments and surgical interventions were recorded retrospectively from patients' files.
Results: Nineteen patients were included in the study, of which 7 (37%) had factor X deficiency, 5 (25%) had factor XI, 3 (16%) had factor V+VIII, 2 (10%) had factor V and 1 (5%) had factor I and XIII deficiencies. Parents of 12 patients had consanguinity marriages. All patients with factor X deficiency had bleeding episodes, and three of them were under prophylaxis with prothrombin complex concentrate. Other patients were under on-demand treatment. In total, 19 surgical interventions (11 minor; 8 major) were performed.
Conclusion: Rare bleeding disorders are very uncommon and heterogeneous, with variable associations between coagulation factor activity and bleeding phenotype. A multidisciplinary and expertise team (haematologists, nurses, gynaecologists, obstetricians, orthopaedist, etc.) is necessary for the treatment and regular follow-up of patients with rare bleeding disorders.

Keywords
Rare factor deficiencies, clinic, treatment, surgery

Anahtar Kelimeler
Nadir faktör eksiklikleri, klinik, tedavi, cerrahi

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Öz

Amaç: Kanama insan hayatındaki en önemli sorunlardan bir tanesidir. Koagülasyon sisteminde yer alan faktörlerin eksikliği, yokluğu veya fonksiyon bozukluğu uzamış kanama, morbidite ve mortaliteye sebep olmaktadır. Faktör eksikliklerinin büyük çoğunluğu faktör VIII, faktör IX ve von Willebrand faktör eksikliği olup diğer faktör eksiklikleri nadir faktör eksiklikleri olarak adlandırılır. Bu çalışmada, nadir faktör eksikliği olan hastaların klinik özellikleri, laboratuvar bulguları, tedavileri ve uygulanan cerrahi girişimler sunulmuştur.
Gereç ve Yöntemler: Çocuk hematolojisi ve onkolojisi bilim dalında Temmuz 1997 ve Haziran 2020 tarihleri arasında takip edilen faktör VII eksikliği dışında nadir faktör eksikliği tanısı alan hastalar çalışmaya dahil edildi. Hastaların demografik özellikleri, klinik bulguları, aile hikayeleri, protrombin zamanı/aktive parsiyel

tromboplastin zamanı ve faktör düzeyleri ile tedavileri ve cerrahi girişimler hasta dosyalarından retrospektif olarak tarandı.
Bulgular: On dokuz hasta çalışmaya dahil edildi. Yedi hasta (%37) faktör X, 5'i (%25) faktör XI, 3'ü (%16) faktör V + faktör VIII, 2'si (%10) faktör V ve 1'er (%5) hasta faktör I ile faktör XIII eksikliği tanısı almıştı. On iki hastanın ebeveynlerinde akraba evliliği vardı. Faktör X eksikliği olan tüm hastaların kanama hikayesi olup 3 hasta protrombin kompleks konsantresi ile profilaksi tedavisi almakta ve diğer hastalar kanadıkça tedavi almaktaydı. Toplam 19 cerrahi girişim uygulanmış olup bunların 11'i minör, 8'i majör cerrahi girişimdi.
Sonuç: Nadir faktör eksiklikleri çok nadir hastalıklar grubundan olup değişik tablolarda karşımıza çıkmaktadırlar. Mevcut olan faktör düzeyi ve klinik arasında her zaman bir korelasyon bulunmamaktadır. Bu nedenle nadir faktör eksikliği olan hastalar multidisipliner (hematoloji, hemşire, jinekoloji, ortopedi...) ve deneyimli ekiplerin olduğu merkezlerde düzenli takip ve tedavi edilmelidir.

Introduction

Bleeding is one of the most important problem in human's life and the coagulation system, which is very complex plays a role to stop bleedings (1). Absence, deficiency or dysfunctions of factors which are the proteins in coagulation system can cause prolonged bleeding, morbidity or mortality (1). Although the majority of factor deficiencies consist of factor VIII (hemophilia A), factor IX (hemophilia B) and von Willebrand factor, all other factor deficiencies called as rare factor deficiencies. Inherited quantitative or qualitative deficiencies of coagulation factors such as factor I (fibrinogen-FI), factor II (FII), factor V (FV), combined FV and factor VIII (FVIII), factor VII (FVII), factor X (FX), factor XI (FXI), factor XIII (FXIII), and vitamin K-dependent clotting factors (FII, FVII, FIX, FX) called as rare bleeding disorders (RBDs) (2). The deficiency of any of the coagulation factors may result in a coagulopathy leading to bleeding episodes (3,4). Hemophilia A (FVIII) and B (FIX) and together with von Willebrand disease, they account for 95% to 97% of all coagulopathies (5,6), however RCDs are much less prevalent, ranging from case in 500,000 to 1 in 2 million in the general population and it could be vary by country (7). Prevalence of RBDs increases in regions with a high rate of consanguinity marriages (3, 4). The diagnosis of these disorders is challenged due to their rarity and clinical heterogeneity. Additionally, treatment guidelines of RBDs is challenging (3). In this study, we present the clinical presentations, laboratory findings, treatments, and surgical interventions in patients with RBDs other than FVII deficiency followed up in our clinic.

Materials and Methods

Patients who were diagnosed as having rare factor deficiency other than FVII in İstanbul University Oncology Institute, Department of Pediatric Hematology and Oncology between July 1997 and June 2020, were included in the study. Patients with FVII deficiency were excuded due to reported in another study (8). The patients' demographic characteristics, clinical presentations, family history, prothrombin time, activated partial thromboplastin time, and factor levels, and treatments and surgical interventions were recorded retrospectively from the patients' files. Clinical bleeding episodes were classified into four categories (Table 1) (2).

Surgical interventions were classified as major and minor surgical interventions. Orthopedic, cardiovascular, neurologic system interventions, and open abdominal surgery are major surgical interventions, whereas endoscopic procedures, biopsy procedures, and dental procedures are minor surgical interventions. Type of surgical intervention, treatment modality, and post-operative complications (bleeding, infection, mortality with rates higher than expected) were recorded. Formal statistical analysis were not performed due to the small sample size in the study.

The study was approved by İstanbul University Oncology Institute Local Academic Board (protocol

Table 1. Clinical bleeding severity in rare bleeding disorders

Bleeding severity	Definition
Asymptomatic	No bleeding episode
Grade I	Trauma or drug ingestion (antiplatelet or anticoagulant therapy) releated bleeding
Grade II	Minor bleedings; mucocutenous bleedings (bruising, ecchymosis, oral cavity bleeding, epistaxis, menorrhagia)
Grade III	Major bleedings; soft tissue hematoma, hemarthrosis, CNS, GI and umbilical cord bleeding

CNS: Central nervous system, GI: Gastrointestinal

no: 109419, date: 02.07.2020) and informed consent was obtained from parents or legal guardians before enrollment in the study.

Results

Nineteen patients were included in the study. Seven (37%) of 19 were FX deficiency, 5 (25%) were FXI, 3 (16%) were FV+FVIII, 2 (10%) were FV deficiencies and 1 (5%) of them FI and FXIII deficiencies. Twelve patient's parents had consanguinity marriages. The demographic characteristics and laboratory results of the study population are shown in Table 2**.**

All patients with FX deficiency had bleeding episodes that 4 had Grade II, 1 had Grade III bleeding episodes. Three of them (#10, #12 and #13) under

Table 2. Demographics, clinical and laboratuary findings in rare bleeding disorders

No (#)	Gender	Type of deficiency	Diagnosis age (years)	Current age (years)	Diagnosis age (years)	Family history/ consanguinity of parents	Clinical presentation	PT (s)	aPTT (s)	Factor level (%)
1	F	FI	1 month	9	1 month	Absent/present	Bleeding of blood-flow area	180	120	<15 mg/ dL*
2	F	FV	10	12	10	Absent/absent	None	14.3	40.4	24.7
3	M	FV	5 months	1,5	5 months	Absent/present	Epistaxis, gingivorragia	51	7	0.1401
4	M	FV+VIII	24	32	24	Present/present	Epistaxis	15.5	41.7	FV=16 FVIII=17
5	F	FV+VIII	35	43	35	Absent/absent	Epistaxis, gingivorragia, menorrhagia	21.9	73.9	FV=4 FVIII=14.7
6	M	FV+VIII	2	6	2	Absent/absent	Gingivorragia	23.6	70.8	FV=4.1 FVIII=3.2
7	F	FX	4	30	4	Present/present	Epistaxis, gingivorragia, menorrhagia	141.8	70.4	2
8	M	FX	2	8	2	Present/present	Epistaxis	20.5	47.3	12.1
9	M	FX	3	17	3	Present/present	Epistaxis, hematuria	17	48	7.4
10	M	FX	3 months	15	3 months	Present/present	CNS bleeding, GI bleeding	14.1	102	1
11	M	FX	4	5	4	Present/absent	Epistaxis	16.5	40.5	58
12	M	FX	3	12	3	Present/present	Epistaxis, gingivorragia	48	65	0.5
13	M	FX	3 months	Exitus	3 months	Present/present	Epistaxis	23.7	45.6	0.5
14	M	FXI	1 month	8	1 month	Present/absent	None	11.6	62	6
15	M	FXI	20	39	20	Present/present	Wound bleeding	11.8	56	0.9
16	F	FXI	19	30	19	Present/present	Prolonged bleeding, menorrhagia	14.7	70.2	3.38
17	M	FXI	1	3	1	Absent/absent	None	11.8	43.5	21
18	M	FXI	4	15	4	Absent/absent	Hemoptysis	13	44.5	22
19	M	FXIII	1	9	1	Present/present	Umblical cord bleeding, ecchymosis	13.3	34.4	1.11

CNS: Central nervous system, GI: Gastrointestinal, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, *Fibrinogen level mg/dL, F: Female, M: Male

prophylaxis with prothrombin complex concentrate (PCC). One (#10) had central nervous system (CNS) bleeding and others (#12 and #13) who were also brothers had uncontrolded epistaxis. Other patients were under on-demand treatment.

Totally, 19 surgical interventions were performed. Eleven of them minor and 8 were major. Hemostasis plan was prepared according to patient's factor level, bleeding tendency and type of operation (Table 3).

Discussion

RBDs are a heterogenous group of diseases that result from deficiencies of a coagulation proteins and affect both males and females and inherited as autosomal recessive. There is no clear consensus in terms of treatment due to rarity, in contrast to hemophilia. Factor concentrates are available for FI, FVII, FX, FXI, FXIII and most of them are plasma derived factor concentrates; recombinant factor concentrates are only avaible for FVII and FXIII (4). For other RBDs PCCs, fresh frozen plasma (FFP) and cryoprecipitate are the treatment choices (3,4,9).

Available information on the worldwide data of RBDs from World Federation of Haemophilia Global Survey showed that FVII and FXI deficiencies are the most common RBDs and followed by the deficiencies of fibrinogen, FV and FX, FXIII and more rare FII and combined FV + FVIII deficiencies (10). These results were similar with the report of European Network of RBDs (2). In the present study, most common deficiencies were FX and FXI followed by FV+FVIII, FV, FI and FXIII deficiencies.

Fibrinogen deficiency may be either quantitative or qualitative. However, the most common symptom of afibrinogenemia is mucocutaneous bleedings, soft tissue bleeding, joint bleeding and prolonged bleeding from the umbilical stump could be seen. Additionally, spontaneus CNS bleedings could be the cause of death (3,11). In the present cohort, 1 patient was recorded as afibrinogenemia and she was diagnosed after birth

Table 3. Surgical interventions in rare bleeding disorders

No	Type of deficiency	Age of surgical procedure (years)	Type of surgery	Treatment	Complication
4	FV+FVIII	29	Dental interventions	FFP+FVIII	None
		29	Total thyroidectomy		None
5	FV+FVIII	38	Dental interventions	FFP+FVIII	None
		43	Thyroid biopsy	FFP+FVIII	None
7	FX	24	Dental intervention	PCC	None
		28	C/S	PCC	None
		29	Dental interventions	PCC	None
		30	Dental interventions	PCC	None
8	FX	3	Eyelid cyst excision	PCC	None
10	FX FX	9	Tooth extraction	PCC	None
		10	Tooth extraction	PCC	None
11	FX	4	Circumcision	FFP	None
12	FX	6	Adenodectomy	PCC	None
		6	Tooth extraction	PCC	None
		9	Tooth extraction	PCC	None
13	FX	3	Congenital nevus excision-maling melanoma	PCC	None
15	FXI	38	Inguinal hernia operation	FFP	None
17	FXI	3	Adenodectomy	Tranexamic acid	None
18	FXI	8	Circumcision	Tranexamic acid	None

C/S: Cesarean/section, FFP: Fresh frozen plasma, PCC: Protrombin complex concentrate

due to bleeding from blood-flow areas. Additionally, she is still under prophylaxis by fibrinogen concentrate and had no major bleeding episode. The patients can suffer from pain of unknown origin in their limbs due to cystic intraosseous lesions (12).

Mucosal bleedings are the most common bleeding types of FV deficiency. Life-threatening bleedings such as CNS bleeding, gastrointestinal (GI) bleeding, hemarthrosis are rarely seen in FV deficiency (13). Several mutations including missense, nonsense, frameshift, and splice sitemutations have been reported for FV deficiency (14). Factor V deficiency of this cohort (Table 1, #3) had homozygous, missense mutation in *FV* gene [c.(6197G>A);(6197G>A) p.(Cys2066Tyr)] and had severe form with frequent nose and gum bleeding episodes. On the other hand, other patient (Table 1, #2) had mild type and had no bleeding episode.

Combined FV+FVIII deficiency, characterized by concomitantly low levels of the two coagulation factors and is associated with a mild bleeding to moderate bleeding tendency, being together does not increase the bleeding tendency (15,16). Additionally, other bleeding types include bleeding after surgery, dental extraction and trauma (16). Combined FV+FVIII deficiency is totally different from FV deficiency and FVIII deficiency that this disease should not be thought as the same disease. The treatment of FV and FVIII deficiency is usually on-demand and FFP together with FVIII concentrate is used accoding to plasma factor levels (3,4,16). In the present cohort, 3 patients were diagnosed with FV and FVIII deficiency and all had mild bleeding symptoms such as epistaxis, gum bleeding and menorrhagia same as described patients in the literature. Two patients had surgical interventions and had no complication after surgery. Two of them received FFP and FVIII concentrate according to their factor levels and bleeding phenotype.

Most common bleeding symptom is epistaxis in factor X deficiency and patients may present severe bleeding symptoms such as CNS, or GI bleeding and hemarthroses or hematomas. Additionally, menorrhagia is common symptom of women with FX deficiency (3,17,18). The majority of our cohort was FX deficiency and 6 of 7 patients had epistaxis and 1 women had menorrhagia. One severe FX deficiency patient (Table 1, #10) had intracranial hemorrhage and GI bleeding. Miscarriage, uterine bleeding, postpartum hemorrhage and preterm labor could be seen during pregnancy (19). In the present study, the patient (Table 2, #7) had miscarriage and had cesarean/section. For the treatment of bleeding episodes, surgery and prophylaxis of FX deficiency, plasma derived FX concentrate or plasma-derived products such as PCC that also contain other clotting factors could be used (3,17,20). All bleeding episodes and also surgical interventions were treated with PCC due to inavaibility of plasma derived FX concentrate in this study. The patient (Table 2, #13) who had congenital nevus diagnosed as malign melonoma had multiple surgical interventions of lesions and died due to progression of malignancy (21).

Bleeding phenotype is not correlated with plasma FXI level (22). Although, patients with the severe deficiency are at a higher risk of bleeding, they may remain asymptomatic and partial deficient patients may bleed after trauma or surgery (3,23). Antifibrinolytics, FFP and plasma-derived-FXI concentrate could be used for the treatment of FXI deficiency (3). In our patients, no major bleeding was recorded although low levels of FXI and 2 patients had surgical interventions with FFP or tranexamic acid due to inavaibility of FXI concentrate.

The first symptoms of FXIII deficiency are umbilical cord bleeding and soft tissue hematoma. Symptoms of FXIII deficiency range from life-threatening bleeding to mild forms of bleeding (24-27). Only 1 patient had FXIII deficiency in our study and his factor level was low and he had umblical cord bleeding in his history. Plasma-derived-FXIII concentrate has been shown to be safe and effective. Hovewer, FXIII concentrate is not available, cryoprecipitate should be preferred to FFP due to higher FXIII content as in our country (3,28).

Conclusion

RBDs are very rare and heterogeneous, with variable associations between coagulation factor activity and bleding phenotype. A multidisciplinary and expertise team (hematologists, nurses, gynecologists and obstetricians, orthopedics etc.) is necessary for the treatment and regular follow-up of the patients with RBDs.

Ethics

Ethics Committee Approval: The study was approved by İstanbul University Oncology Institute

Local Academic Board (protocol no: 109419, date: 02.07.2020).

Informed Consent: Informed consent was obtained from parents or legal guardians before enrollment in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.Z., B.K., Design: B.Z., B.K., Supervision: B.Z., B.K., Fundings: B.Z., B.K., Data Collection or Processing: B.Z., B.K., Analysis or Interpretation: B.Z., B.K., Literature Search: B.Z., B.K., Critical Review: B.Z., Writing: B.K.

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Original Article / Özgün Araştırma

Evaluation of Pharyngeal Airway Volume in Individuals with Different Skeletal Patterns

Farklı İskelet Yapısına Sahip Bireylerde Faringeal Havayolu Hacminin Değerlendirilmesi

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Keywords
Oropharyngeal airway, nasopharyngeal airway, cone-beam computed tomography, skeletal pattern

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Abstract

Objective: This retrospective study aimed to evaluate and compare the airway shape and volume using cone-beam computed tomography (CBCT), which allows three-dimensional examination of the airway in individuals with different skeletal patterns.

Materials and Methods: For this retrospective study, a total of 235 CBCT images were selected from the archives of Dicle University Faculty of Dentistry Department of Oral Diagnosis and Radiology. Selected CBCTs were first divided into three groups according to their ANB angles: Class I (0<ANB<4), Class II (ANB>4) and Class III (ANB<0). Each group was further divided into three subgroups: low angle [SNGoGn<28, sum of posterior angles (SPA)<393], normal angle (28<SNGoGn<36, 393<SPA<399) and high angle (SNGoGn>36, SPA>399) according to SNGoGn and SPA. The total airway volume, oropharyngeal airway volume, nasopharyngeal airway volume, axial area at C2 and C3 vertebra levels, minimum axial area, axial area at the border of the oropharynx and nasopharynx and the transverse and anteroposterior lengths of each area were measured. Kruskal-Wallis variance analysis was used in between-group comparisons. Correlations between variables were tested with the Pearson correlation coefficient.

Results: Statistically significant differences in the oropharyngeal airway and total airway were found between Class I and Class II and between Class II and Class III ($p<0.01$). A statistically significant difference in the total airway volume was noted between the low angle and high angle subgroups of Class I, Class II and Class III ($p<0.05$).

Conclusion: The oropharyngeal, nasopharyngeal and total airway volumes of patients with Class II were smaller than those with Class I and Class III. Individuals with high angle vertical skeletal pattern were found to have smaller total airway volume than those with a low angle vertical skeletal pattern.

Öz

Amaç: Bu retrospektif çalışmanın amacı, farklı iskelet yapısına sahip bireylerde havayolunun 3-boyutlu incelenmesine olanak veren konik ışınlı bilgisayarlı tomografi (KIBT) yardımıyla havayolu şeklini ve hacmini değerlendirmek ve karşılaştırmaktır.

Gereç ve Yöntemler: Bu retrospektif çalışmada Dicle Üniversitesi Diş Hekimliği Fakültesi Ağız Diş ve Çene Radyolojisi Anabilim Dalı arşivinden toplam 235 KIBT görüntüsü seçildi. Seçilen KIBT'ler ilk olarak ANB açılarına göre Sınıf I (0<ANB<4), Sınıf II (ANB>4) ve Sınıf III (ANB<0) olmak üzere üç gruba ayrıldı. Her grup SNGoGn açısı ve posterior açılar toplamına (PAT) göre üç alt gruba ayrıldı: Kısa (SNGoGn<28, PAT<393), normal (28<SNGoGn<36, 393<PAT<399) ve uzun (SNGoGn>36, PAT>399). Toplam havayolu hacmi, orofaringeal hava yolu hacmi, orofaringeal havayolu hacmi, nazofaringeal havayolu hacmi, C2 ve C3 vertebra seviyelerinde aksiyal alan, minimum aksiyal alan, orofarinks ve nazofarinks sınırında aksiyal alan ve her alanın transversal ve anteroposterior uzunluğu ölçüldü. Gruplar arası karşılaştırmalarda Kruskal-Wallis varyans analizi kullanıldı. Değişkenler arasındaki korelasyonlar Pearson korelasyon katsayısı ile test edildi.

Bulgular: Orofaringeal havayolu ve toplam havayolunda Sınıf I ve Sınıf II grupları ile Sınıf II ve Sınıf III grupları arasında p<0,01 düzeyinde istatistiksel olarak anlamlı farklılıklar bulundu. Sınıf I, Sınıf II ve Sınıf III gruplarının kısa ve uzun alt grupları arasında toplam havayolu hacminde p<0,05 düzeyinde istatistiksel olarak anlamlı farklılık vardı.

Sonuç: Sınıf II hastaların orofaringeal, nazofaringeal ve toplam havayolu hacimleri, Sınıf I ve Sınıf III hastalardan daha küçüktü. Uzun yüz yapısına sahip bireylerin, kısa yüz yapısına sahip olanlara göre daha küçük toplam havayolu hacmine sahip oldukları bulundu.

Introduction

Obstructive sleep apnea (OSA) is a form of sleep-disordered breathing that has a high prevalence rate and is often underdiagnosed. Although it has been known for years, its importance for individuals and society has recently come to the fore. Upper airway narrowing is also considered a risk factor for OSA (1). Due to close relationship between pharyngeal structures and both craniofacial structures, a mutual interaction between pharyngeal structures and dentofacial pattern is expected. Therefore, the relationship between airway volume and facial morphology has long been a subject of debate, and there is a general view that oropharyngeal and nasopharyngeal structures play a role in the development of the dentofacial complex (2-7).

Most of the previous researchers (2-6,8-11) analyzed the relationship between facial morphology and pharyngeal airway shape on 2-dimensional (2D) cephalometric radiographs. However, the problem with 2D radiographs is that they do not allow assessment of pharyngeal volumes. The human airway is 3-dimensional (3D) and therefore lateral films represent 3D structure in 2D. Therefore, previous studies were limited due to analyzing a 3D structure in 2D (12). Lateral cephalometric radiographs also have severe limitations in distortion, magnification, superimposition, and low reproducibility (13).

The diagnostic capacity of the airway has expanded with the development of computed tomography (CT) 3D technology; however, there is an important limitation in the routine use of CT devices due to the high radiation dose they generate. The radiation dose has been reduced thanks to the development of cone-beam computed tomography (CBCT). CBCT has become an accepted craniofacial imaging technique, especially known for its low radiation dose and faster image acquisition times compared to conventional CT (14).

The aim of this retrospective study is to evaluate and compare airway shape and volume with the help of CBCT, which allows the 3D examination of the airway in individuals with different skeletal pattern. Most or the previous studies were based on the sagittal craniofacial pattern and upper pharyngeal airway. This study focused on both sagittal and vertical skeletal pattern with extended sample size.

Materials and Methods

This retrospective study protocol was approved by the Local Ethics Committee in Dicle University Faculty of Dentistry (decision no: 5, date: 01.12.2014). Patients were not given additional radiation for the purpose of this study. CBCT scans were performed for better diagnosis of dental problems, and all patients or parents signed an informed consent form allowing the use of these records. One thousand and three hundred CBCT scans in the archives of Dicle University Faculty of Dentistry Department of Oral Diagnosis and Radiology were evaluated and CBCT scans of 235 individuals (114 girls, 121 boys) who met the inclusion criteria were selected. Our exclusion criteria for research were: detectable pathology along the upper airway, missing teeth except third molars, previous orthodontic treatment or orthognathic surgery, craniofacial syndrome and cleft lip and palate, adenoidectomy or tonsillectomy, CBCT scan age less than 16, nasal obstruction and scans showing incomplete view of the upper airway.

Selected CBCTs were first divided into three groups according to their ANB angles, Class I (0<ANB<4), Class II (ANB>4) and Class III (ANB<0). Each group is divided into three subgroups, low angle (SNGoGn<28, sum of posterior angles (SPA)<393), normal angle (28<SNGoGn<36, 393<SPA<399) and high angle (SNGoGn>36, SPA>399) according to SNGoGn and SPA. The male-female composition of the individuals included in this study by groups and subgroups are shown in Table 1.

All selected CBCT images were acquired with an i-CAT (Imaging Sciences International, Hatfield, Pa) device with 5.0 mA, 120kV, 0.3 mm voxel thickness, a single 360° rotation and 9.6 seconds setting. All data were collected and measured by the same researcher (Y.A.U). All skeletal and airway measurements were done with Dolphin 3D (version 11, Dolphin imaging & Management Solutions, Chatsworth, Calif), a third-party software program.

Total airway volume (TAV), oropharyngeal airway volume (OAV), nasopharyngeal airway volume (NAV), axial area at C2 and C3 vertebra levels, minimum (min) axial area, axial area at the border of the oropharynx and nasopharynx, and the transverse and anteroposterior (AP) length of each area were measured for 3D airway analysis on the CBCT data. The posterior border of the TAV is the posterior pharyngeal wall, the anterior border is the anterior pharyngeal wall, the lower border is the line passing through the lowest and the furthest level of vertebra C3 and parallel to the Frankfurt horizontal plane. When viewed from the sagittal aspect, the upper border is determined as the line that will contain the radiolucent region remaining posteriorly in the section where the dorsal region of the vomer meets the palate (Figure 1). The upper boundary of the OAV is defined as the line that passes through the lowest and foremost end of the Atlas and runs parallel to the Frankfurt Horizontal plane. The lower border is the line passing through the lowest and foremost level of vertebrae C3 and parallel to the Frankfurt Horizontal plane, the posterior border is the posterior pharyngeal wall and the anterior border is the anterior pharyngeal wall (Figure 2). NAV was calculated as the volume obtained by subtracting the OAV from the TAV.

Statistical Analysis

SPSS 15.0 (SPSS Inc., Chicago, IL, USA) statistical package program was used to analyze the data obtained in our study. Statistical significance was set at 0.05. Chi-square test was used to check the distribution of gender in balance between groups. Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. One-Way ANOVA analysis was used to comparisons between groups with normally distributed parameters. Kruskal-Wallis variance analysis was used as a statistical method for comparing the groups for parameters that did not show normal distribution. The Mann-Whitney U test with Bonferroni correction was used for parameters that showed statistically significant differences according to the analysis results. Correlations between variables were tested with the Pearson correlation coefficient.

Images were re-measured 3 weeks after the first measurements for reliability purposes. Dahlberg's

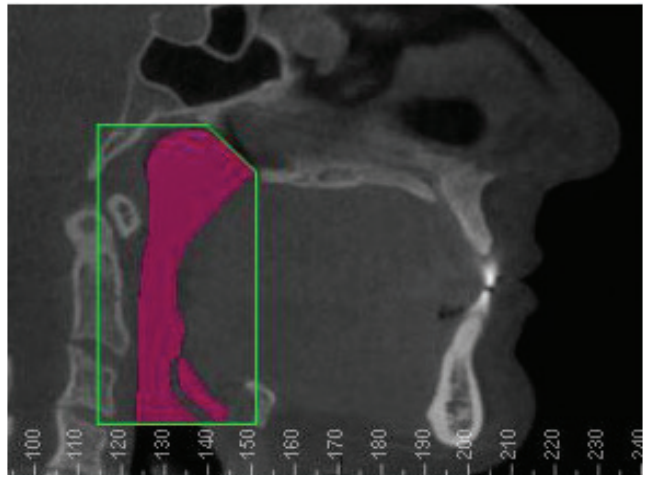

Figure 1. Total airway volume borders

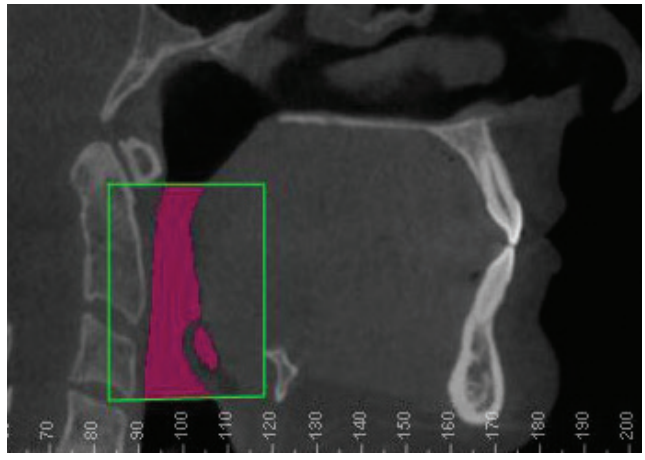

Figure 2. Oropharyngeal airway volume borders

formula ($V\sum d^2/2n$) for linear, areal and angular measurements and the intra-class correlation coefficient (ICC) for volumetric measurements were used to test reliability (15).

Results

In the evaluation of operator calibration, it was confirmed that the ICC results were between 0.928-0.941, and the results of Dalhberg's formula were between 0.354 and 0.802 for all variables evaluated.

The gender distributions of the groups are given in Table 1. The chi-square test was used to check the balanced distribution of gender among the groups. In the groups of this study, we could not find any differences between the groups due to the similar male-female composition and the data were combined because there was no significant difference. As we used ANB, SnGoGn and SPA to form the groups, it was expected to have statistically significant differences on skeletal variables between the groups ($p<0.001$).

Descriptive statistics showing means, standard deviations, min and maximum values for different groups and the results of their comparison are shown in Table 2 ($p<0.05$). There were statistically significant differences between Class I and Class II groups, Class II and Class III groups in terms of OAV, NAV, TAV, cross-sectional area at the C3 level, and min axial area. C3 T and C3 AP lengths differ significantly between Class II and Class III groups ($p<0.05$); min axial AP length between Class I and Class II groups ($p<0.05$); however, no difference was found in other length parameters.

Statistically significant differences were found between the low angle and high angle subgroups of Class I group in terms of OAV and TAV ($p<0.05$). Statistically significant differences at $p<0.05$ level were found between the low angle and high angle subgroups of the Class I group and the normal angle and high angle subgroups in the cross-sectional area at C2 level. There were statistically significant differences at $p<0.01$ level in terms of C2 AP length between the low angle and high angle, normal angle and high angle subgroups of the Class I group (Table 3). There was a statistically significant difference at the level of $p<0.05$ in TAV between the low angle and high angle subgroups of Class II and Class III groups (Tables 4, 5).

Bivariate correlations are given in Table 6. Negative correlations were found between volumetric measurements and ANB, SNGoGn and SPA. In addition, negative correlations were found between C2, min and O-N border AP length measurements, SNGoGn and SPA. A high correlation was found between the min axial cross-sectional area and volumetric measurements. A positive correlation was found between OAV and NAV.

Discussion

There are few studies examining the pharyngeal airway with 3D techniques in Class I, Class II and Class III skeletal malocclusions with different vertical skeletal pattern. Whereas, understanding the anatomy of individuals with different craniofacial growth patterns and the nature of this region may create new opportunities for the development of treatment plans and treatment methods.

Table 1. Male-female composition of Class I, Class II and Class III groups and their subgroups

Group	Female	Male	Sum	Subgroup	Female	Male	Sum	p
Class I	42	40	82	High angle	14	14	28	>0.10
				Normal angle	14	14	28	
				Low angle	14	12	26	
Class II	40	43	83	High angle	12	14	26	
				Normal angle	14	15	29	
				Low angle	14	14	28	
Class III	32	38	70	High angle	11	13	24	
				Normal angle	10	12	22	
				Low angle	11	13	24	
Sum	114	121	235		114	121	235	

Table 2. Descriptive statistics showing the means, standard deviations, minimum and maximum values of the Class I, Class II and Class III groups and results of intergroup comparisons using Kruskal-Wallis test

	Class I				Class II				Class III				I-II	I-III	II-III
	n	Mean ± SD	Min	Max	n	Mean ± SD	Min	Max	n	Mean ± SD	Min	Max		p	p
Volumetric (mm^3)															
OAV	82	11296.51±4475.99	4483.90	21374.80	83	9240.28±2489.81	2929.7	23110.2	70	11427.97±2887.77	3159.70	31943	**	NS	**
NAV	82	11192.44±3737.70	3771	22051	83	9423.65±3767.87	1297.3	21806.1	70	10693.53±3509.48	2385	24239.70	**	NS	*
TAV	82	22488.94±7407.03	10655.20	41025.90	83	18663.93±5232.03	6998	44916.3	70	22121.50±5997.42	6635.10	44749.3	**	NS	**
Cross-sectional (mm^2)															
C2	82	247.76±118.90	54.70	563.50	83	219.64±119.11	40.70	620.2	70	240.35±106.38	60.30	506.70	NS	NS	NS
C3	82	268.64±117.56	75.60	589.60	83	222.98±108.49	54.60	641.10	70	269.32±131.21	66.40	707.10	*	NS	*
MinAx	82	202.59±94.71	50	441.7	83	157.68±82.04	33.1	421.9	70	175.48±78.69	57.40	407.20	**	NS	*
OP-NP border	82	303.26±110.8	86.7	565.8	83	278.08±118.91	46.5	569.2	70	293.99±120.14	59.20	735.90	NS	NS	NS
Length (mm)															
C2 T	82	25.19±6.59	10.59	38.28	83	24.41±7.02	10.30	40.30	70	26.8±7.16	10.41	50	NS	NS	NS
C2 AP	82	10.94±3.58	3.57	20	83	10.21±3.07	3.49	19.43	70	11.23±3.72	4.31	19.67	NS	NS	NS
C3 T	82	29.38±5.2	14.44	40.54	83	28.39±5.61	14.14	40.42	70	30.67±6.19	16.33	51	NS	NS	*
C3 AP	82	11.73±4.36	3.90	22.12	83	10.33±3.83	3.08	21.67	70	12.03±4.47	4.35	26.88	NS	NS	*
MinAx T	82	23.22±6.03	10.54	39.94	83	23.38±6.30	10.59	30.54	70	23.56±6.08	7.14	36.56	NS	NS	NS
MinAx AP	82	9.43±3.01	3.20	15.11	83	8.05±2.99	2.65	17.58	70	8.33±3.03	2.59	15.71	*	NS	NS
OP-NP border T	82	29.2±6.61	14.86	44.44	83	27.18±7.46	10.70	50.88	70	28.79±6.42	13.96	42.5	NS	NS	NS
OP-NP border AP	82	12.08±3.47	6.46	22.96	83	11.26±3.38	4.23	20.5	70	12.30±4.03	4.79	30	NS	NS	NS

NAV: Nasopharyngeal airway volume, OAV: Oropharyngeal airway volume, TAV: Total airway volume, OP: Oropharynx, NP: Nasopharynx, minAx: Minimum area of the oropharynx on the axial slice, T: Transversal, AP: Anteroposterior, I: Class I, II: Class II, III: Class III, SD: Standard deviation; min: Minimum, max: Maximum, NS: Not significant, *p<0.05, **p<0.01, ***p<0.001

Table 3. Descriptive statistics of Class I subgroups showing means and standard deviations of volumetric, cross-sectional, and length variables, and comparison of these measurements according to vertical skeletal pattern

Class I									
	Low angle		Normal angle		High angle		L-N	L-H	N-H
Volumetric (mm^3)	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	p	p	p
OAV	28	12386.62±4640.58	29	11766.08±5855.47	26	9736.83±3570.29	NS	*	NS
NAV	28	11646.36±3426.18	29	11640.37±3958.44	26	10290.59±3752.73	NS	NS	NS
TAV	28	24032.98±7308.16	29	23406.45±8111.74	26	20027.39±6311.91	NS	*	NS
Cross sectional (mm^2)									
C2	28	279.29±134.83	29	261.67±109.52	26	202.32±102.59	NS	*	*
C3	28	286.89±143.75	29	272.34±93.74	26	246.69±109.29	NS	NS	NS
MinAx	28	204.21±100.21	29	198.10±98.29	26	205.46±82.41	NS	NS	NS
OP-NP border	28	301.91±118.99	29	294.52±96.19	26	313.35±113.94	NS	NS	NS
Length (mm)									
C2 T	28	25.55±6.49	29	25.89±6.72	26	24.13±6.64	NS	NS	NS
C2 AP	28	12.19±3.88	29	11.45±3.66	26	9.18±2.51	NS	* *	* *
C3 T	28	30.32±5.53	29	29.15±4.11	26	28.67±5.93	NS	NS	NS
C3 AP	28	11.94±5.19	29	12.42±3.85	26	10.83±4.01	NS	NS	NS
MinAx T	28	22.77±4.33	29	24.08±5.75	26	22.81±7.59	NS	NS	NS
MinAx AP	28	8.78±3.29	29	8.76±3.18	26	10.75±2.53	NS	NS	NS
OP-NP border T	28	30.45±6.67	29	28.85±6.27	26	28.3±6.98	NS	NS	NS
OP-NP border AP	28	13.12±4.04	29	11.96±2.40	26	11.16±3.69	N.S.	N.S.	N.S.

NAV: Nasopharyngeal airway volume, OAV: Oropharyngeal airway volume, TAV: Total airway volume, OP: Oropharynx, NP: Nasopharynx, MinAx: Minimum area of the oropharynx on the axial slice, T: Transversal, AP: Anteroposterior, L: Low angle group, N: Normal angle group, H: High angle group, SD: Standard deviation, NS: Not significant, *p<0.05, **p<0.01, ***p<0.001

Although there are 2D studies in the literature in which airway analyzes of individuals are performed, the number of 3D studies has not yet reached a sufficient level yet (3-6,10). The advantage of this method is that the lateral cephalometric radiography is more common and cheaper than CBCT, and the radiation level is lower. Since the human airway is a 3D dynamic structure, it is not sufficient to examine it statically in 2D. However, there are some disadvantages, such as magnification of the 2D image, distortion, and superimposing of anatomical structures (16). Aboudara et al. (12) reported that CBCT was a simple and effective data for accurate airway analysis in their study comparing the airway measurements obtained with lateral cephalometric radiography and CBCT. In addition, 2D measurements of nasopharyngeal airway area; they found that due to the compression of the 3D structure into the 2D structure, most of the structural information was insufficient. Airway measurements of this study are consistent with the study of Haskell et al. (17).

As is known, the airway is a mobile structure and can exhibit mobility during inhalation. Lowe et al. (13) reported that airway size is related to the respiratory phase. People are routinely instructed to hold their breath during the CBCT scan with the i-CAT device. It is suitable for not breathing due to its short 9.6 seconds scanning time. Thus, the respiratory phase was controlled, a standardization of the images was obtained and at the same time, the airway was kept stable during the scan.

El and Palomo (18) performed 3D measurements of the pharyngeal airway using different software programs and compared the accuracy and reliability

Table 4. Descriptive statistics of Class II subgroups showing means and standard deviations of volumetric, cross-sectional, and length variables, and comparison of these measurements according to vertical skeletal pattern

Class II									
	Low angle		Normal angle		High angle		L-N	L-H	N-H
Volumetric (mm^3)	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p**	**p**	**p**
OAV	24	9838.04±4488.03	22	9475.61±4875.09	24	8407.19±4185.27	NS	NS	NS
NAV	24	10433.59±3254.85	22	9047.91±4962.34	24	8789.45±3939.99	NS	NS	NS
TAV	24	20271.63±6678.80	22	18523.52±8010.50	24	17196.64±6979.50	NS	*	NS
Cross sectional (mm^2)									
C2	24	227.64±122.49	22	239.00±108.11	24	192.28±101.20	NS	NS	NS
C3	24	230.05±124.32	22	233.24±89.32	24	205.65±110.07	NS	NS	NS
MinAx	24	161.98±82.81	22	170.63±91.12	24	140.43±72.81	NS	NS	NS
OP-NP border	24	269.79±87.52	22	281.87±135.34	24	282.58±133.88	NS	NS	NS
Length (mm)									
C2 T	24	23.56±5.27	22	26.44±8.76	24	23.23±6.65	NS	NS	NS
C2 AP	24	10.35±3.55	22	10.91±2.49	24	9.37±2.97	NS	NS	NS
C3 T	24	28.67±5.59	22	29.03±5.51	24	27.47±6.12	NS	NS	NS
C3 AP	24	10.89±4.13	22	10.64±3.20	24	9.46±4.05	NS	NS	NS
MinAx T	24	23.82±6.51	22	23.13±6.89	24	23.19±5.75	NS	NS	NS
MinAx AP	24	8.30±3.33	22	8.30±2.83	24	7.55±2.84	NS	NS	NS
OP-NP border T	24	26.91±7.09	22	27.83±8.95	24	26.8±6.56	N.S.	N.S.	N.S.
OP-NP border AP	24	10.89±2.22	22	11.50±3.34	24	11.39±4.35	N.S.	N.S.	N.S.

NAV: Nasopharyngeal airway volume, OAV: Oropharyngeal airway volume, TAV: Total airway volume, OP: Oropharynx, NP: Nasopharynx, MinAx: Minumum area of the oropharynx on the axial slice, T: Transversal, AP: Anteroposterior, L: Low angle group, N: Normal angle group, H: High angle group, SD: Standard deviation, NS: Not significant, *p<0.05, **p<0.01, ***p<0.001

of these programs. One of the software programs they use is the Dolphin 3D program, and they have reported that it is reliable. In our study, we performed 3D airway analysis using Dolphin 3D software.

In the literature, malocclusion type has no effect on pharyngeal airway width (5,6). When the skeletal classification is examined, it is seen that Class I and Class III individuals have a larger airway volume than Class II individuals. Kim et al. (19) stated that retrognathic individuals tend to have a smaller airway volume in normal anteroposterior relationship compared to those with retrognathic jaws. In our study, we found that the smaller airway volume in Class II skeletal individuals emerged as a result of the retrognathic skeletal structure. Grauer et al. (20) also found similar findings. In the Class II group, the shorter and backward mandible can push the tongue and soft palate into the pharyngeal cavity, resulting in a decrease in the volume of the oropharynx. Kikuchi (21) reported in a 3D airway study that the airway is affected by the skeletal structure of the oropharyngeal region. He stated that the pharyngeal morphology other than the airway size was affected by the anteroposterior relationship of the mandible.

El and Palomo (7), in a study examining the airway in 3D, found that the NAV of Class I individuals was larger than Class II individuals. Kerr (9) stated that individuals with Class II malocclusion have smaller nasopharyngeal and adenoid tissue areas. Researchers have shown that there is a relationship between the upper airway and the type of malocclusion and that the nasopharynx is narrower in individuals

Table 5. Descriptive statistics of Class III subgroups showing means and standard deviations of volumetric, cross-sectional, and length variables, and comparison of these measurements according to vertical skeletal pattern

Class III									
	Low angle		Normal angle		High angle		L-N	L-H	N-H
Volumetric (mm^3)	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**n**	**Mean ± SD**	**p**	**p**	**p**
OAV	28	12088.98±4549.18	28	11711.97±5564.04	26	10482.96±4467.88	NS	NS	NS
NAV	28	11808.89±3548.90	28	10663.86±3508.07	26	9607.84±3193.09	NS	NS	NS
TAV	28	23897.87±7534.68	28	22375.83±6241.54	26	20090.8±6832.01	NS	*	NS
Cross sectional (mm^2)									
C2	28	250.14±110.87	28	239.74±106.80	26	231.17±104.21	NS	NS	NS
C3	28	282.60±134.80	28	280.82±137.96	26	244.54±120.67	NS	NS	NS
MinAx	28	178.66±76.45	28	179.68±84.94	26	168.1±70.80	NS	NS	NS
OP-NP border	28	314.68±144.16	28	295.56±91.29	26	271.73±119.33	NS	NS	NS
Length (mm)									
C2 T	28	26.67±7.42	28	27.05±6.42	26	26.68±7.69	NS	NS	NS
C2 AP	28	11.60±3.74	28	11.43±3.59	26	10.66±3.90	NS	NS	NS
C3 T	28	31.29±7.08	28	30.98±6.43	26	29.74±4.87	NS	NS	NS
C3 AP	28	12.11±4.23	28	13.45±4.43	26	10.53±4.41	NS	NS	Ns
MinAx T	28	23.84±6.17	28	23.84±5.17	26	23±7.03	NS	NS	NS
MinAx AP	28	8.29±3.21	28	8.67±3.01	26	8.03±2.95	NS	NS	NS
OP-NP border T	28	29.85±7.30	28	28.63±4.91	26	27.89±6.89	NS	NS	NS
OP-NP border AP	28	13.54±5.38	28	12.24±2.66	26	11.12±3.21	NS	NS	NS

NAV: Nasopharyngeal airway volume, OAV: Oropharyngeal airway volume, TAV: Total airway volume, OP: Oropharynx, NP: Nasopharynx, MinAx: Minumum area of the oropharynx on the axial slice, T: Transversal, AP: Anteroposterior, L: Low angle group, N: Normal angle group, H: High angle group, SD: Standard deviation, NS: Not significant, *p<0.05, **p<0.01, ***p<0.001

with Class II malocclusion (22,23). Hwang et al. (24) reported that the narrowed nasopharyngeal airway is associated with the retrusive mandible and maxilla. Paul and Nanda (23) found a high prevalence of mouth breathing and nasopharyngeal airway obstruction in individuals with Class II malocclusion. These studies are compatible with our study.

In some studies (5,6,8), no significant difference was found when comparing the upper airways of various individuals. We concluded that these results are due to the small number of cases, the classification being performed as dental instead of skeletal, or 2D studies.

In this study, statistically significant differences were found between the Class I and Class II groups and between the Class II and Class III groups in C3 and min axial cross-sectional areas. There was no difference in other area parameters. In linear measurements, no statistically significant difference was observed in most parameters. The statistically significant differences observed in the volumetric parameters were not similar in all area and linear parameters. We concluded that not every subdivision of the airway represents the entire airway capacity of the individual. The findings of Kim et al. (19) are consistent with this result.

In this study, it was observed that individuals with the high angle vertical skeletal type had a smaller TAV than the low angle type. There was no significant difference in NAV in all three groups and subgroups. Kerr (9), Handelman and Osborne (25) found a weak relationship between facial morphology and the nasopharyngeal airway. These studies are consistent with our findings. de Freitas et al. (6) found that

Table 6. Pearson correlation coefficients for oropharyngeal airway volume, nasopharyngeal airway volume, total airway volume, and MinAx area compared with the variables used for this study

		OAV	NAV	TAV	Minimum axial area
ANB	R	-0.176**	-0.207**	-0.173**	-0.178**
SN-GoGn	R	-0.175**	-0.196**	-0.211**	-0.140*
SIA	R	-0.180**	-0.192**	-0.213**	-0.144*
Age	R	0.047	0.027	0.036	0.007
OAV	R	1	0.513**	0.899**	0.860**
NAV	R	0.513**	1	0.838**	0.523**
TAV	R	0.899**	0.838**	1	0.815**
C2 Area	R	0.895**	0.476**	0.813**	0.843**
C3 Area	R	0.231**	0.316**	0.626**	0.690**
MinAx	R	0.860**	0.523**	0.815**	1
O-N Area	R	0.681**	0.528**	0.703**	0.640**
C2 T	R	0.713 **	0.408**	0.662**	0.632**
C2 AP	R	0.701**	0.311**	0.605**	0.697**
C3 T	R	0.561**	0.244**	0.482**	0.496**
C3 AP	R	0.606**	0.263**	0.520**	0.600**
MinAx T	R	0.712**	0.422**	0.699**	0.693**
MinAx AP	R	0.631**	0.361**	0.586**	0.712**
O-N T	R	0.630**	0.541**	0.678**	0.614**
O-N AP	R	0.436**	0.284**	0.423**	0.377**

NAV: Nasopharyngeal airway volume, OAV: Oropharyngeal airway volume, TAV: Total airway volume, minAx: Minimum area of the oropharynx on the axial slice, SIA: Sum of the inner angles, T: Transversal, AP: Anteroposterior *Correlation is significant at the 0.05 level (2-tailed) **Correlation is significant at the 0.01 level (2-tailed)

individuals with vertical skeletal pattern of Class I and Class II malocclusion had a narrower upper airway than vertically normal Class I and Class II malocclusion individuals. Other 2D studies (26-28) are not in line with our results. These studies were performed to evaluate pharyngeal airway widths on 2D lateral cephalometric films. Airway volume requires complex and dynamic 3D evaluation. There may be different findings due to this situation.

A negative correlation was found between volumetric measurements and ANB angle in the current study. This supports the results of the comparison of different anteroposterior skeletal types between the groups. This negative correlation between ANB angle and volumetric measurements can be explained by the fact that Class I and Class III groups have larger airway volume than Class II group. El and Palomo (7) observed that the oropharyngeal volume is inversely correlated with the ANB angle. Ceylan and Oktay's (5) study is also compatible with our study. Kim et al. (19) showed a negative correlation between the ANB angle and the TAV in their study.

A negative correlation was found between the volumetric measurements and SNGoGn and SPA angles. In addition, a negative correlation was found between C2, minimum and O-N boundary anteroposterior length measurements and SNGoGn and SPA angles. Joseph et al. (2) reported that the hyperdivergetic patients showed narrow pharyngeal dimensions, especially in the nasopharynx at the level of the hard palate, in the anteroposterior direction, and at the level of the soft palate and mandible in the anteroposterior direction. Our results are consistent with studies reporting an inverse relationship between pharyngeal volume and vertical skeletal type (6,29,30). El and Palomo (7) could not find a significant correlation between mandibular plane angle and OAV and NAV. The reason for this different

result may be that El and Palomo (7) excluded severe hypodivergent and hyperdivergent individuals from their work. Contrary to our findings, Kim et al. (19) found a positive correlation between vertical skeletal pattern and values analyzing airway volume. The reason for this discrepancy may be due to the values used to evaluate the vertical skeletal type being less comparable to the different values used.

A high correlation was found between the min axial cross-sectional area and volumetric measurements. Tso et al. (31) also mentioned the high correlation between the narrowest cross-sectional area of the airway and TAV. El and Palomo (7) found a high correlation between OAV and min axial cross-sectional area. Considering the results of our study, we think that the determining the areas with upper airway constriction and understanding the size and volume of the pharyngeal airway are clinically important in treatment planning.

A positive correlation was found between OAV and NAV. Kim et al. (19) found a positive correlation between the nasal airway and the upper pharyngeal airway. El and Palomo (7) also found a positive correlation between NAV and OAV. We think that the positive correlation between the OAV and NAV is due to the use of healthy individuals without airway pathology. Individuals with nasal allergy, craniofacial anomalies, hypertrophic adenoids, and narrowed nasopharyngeal airway space will have pharyngeal contraction inevitable and a negative correlation will be observed (32). Structurally, OAV and NAV are not only anatomically contiguous structures, but also directly related in volume. Therefore, the positive and negative factors that may occur will contribute positively and negatively to the correlation relationship.

Conclusion

Class II individuals have smaller OAV, NAV, TAV and min axial area than Class I and Class III groups. Individuals with high angle vertical skeletal pattern were found to have smaller TAV than those with a low angle vertical skeletal pattern.

Volumetric studies about pharyngeal airway add a new perspective to orthodontic practice. Detailed analysis of airway shape and volume can be an important tool in orthodontic diagnosis and treatment plan. Caution should be taken in this regard, especially in patients with mandibular retrusion, with a tendency to have a smaller oropharyngeal area and volume, and patients with hyperdivergent growth patterns.

Ethics

Ethics Committee Approval: This retrospective study protocol was approved by the Local Ethics Committee in Dicle University Faculty of Dentistry (decision no: 5, date: 01.12.2014).

Informed Consent: All patients or parents signed an informed consent form allowing the use of these records.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.İ.K., Y.A.Ü., Design: M.İ.K., Y.A.Ü., Supervision: M.İ.K., Data Collection or Processing: Y.A.Ü., Analysis or Interpretation: İ.Y., Literature Search: M.İ.K., Critical Review: M.İ.K., Writing: Y.A.Ü.

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Original Article / Özgün Araştırma

Can Dental Anxiety During Impacted Third Molar Surgery Be Measured Biometrically? Clinical Study with the Galvanic Skin Response Technique

Gömülü Üçüncü Molar Ameliyatı Sırasında Dental Anksiyete Biyometrik Olarak Ölçülebilir mi? Galvanik Deri Yanıtı Tekniği ile Klinik Çalışma

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Biometric Data, Dental anxiety, galvanic skin response, patient experience, third molar surgery, electrodermal activity

Anahtar Kelimeler
Biyometrik veri, dental anksiyete, galvanik deri yanıtı, hasta deneyimi, üçüncü molar cerrahi, elektrodermal aktivite

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Abstract

Objective: The present study aimed to define the experience and stages of dental anxiety in oral and maxillofacial surgery patients using real-time biometric data collection tools.

Materials and Methods: In this study, the patient-dentist interaction was divided into three sessions: The pre-surgery, oral surgery and post-surgery sessions. A software algorithm was used to record the galvanic skin response signals and heart rate data of patients when they sat on the dental chair for a tooth extraction procedure.

Results: A total of 38 patients with a mean age of 24.8 years were included in the study. Fifteen of the participants were men (39.5%) and 23 were women (60.5%). In the operative phase, which is the second of the three oral surgery phases, there was a statistically significant difference between the mean values of the op galvanic skin response and op heart rate ($p<0.001$).

Conclusion: Emotional/motivational changes during the oral surgery stages can be determined through biometric data analysis. The measurement of biometric parameters, combined with the dentist's experience, can enable the dentist to make decisions about preferable procedures and approaches in the treatment of patients with dental anxiety.

Öz

Amaç: Bu çalışmanın amacı, gerçek zamanlı biyometrik veri toplama araçlarını kullanarak ağız, diş ve çene cerrahisi hastaların, dental anksiyete deneyimi ve aşamalarını tanımlamaktır.

Gereç ve Yöntemler: Çalışma protokolü ameliyat öncesi, ameliyat ve ameliyat sonrası olmak üzere üç bölüme ayrıldı. Hastaların diş çekimi prosedürü sırasında galvanik deri tepki sinyallerini ve kalp atış hızı verilerini kaydetmek için bir yazılım algoritması kullanıldı.

Bulgular: Çalışmaya ortalama yaşı 24,8 yıl olan 38 hasta dahil edildi. Katılımcıların 15'i erkek (%39,5), 23'ü kadındı (%60,5). Çalışmanın ameliyat bölümü operasyon fazında galvanik deri yanıtı ve kalp atış hızı ortalama değerleri arasında istatistiksel olarak anlamlı fark vardı (p<0,001).
Sonuç: Ağız cerrahisinin aşamalarındaki duygusal/motivasyonel değişiklikler biyometrik veri analizi ile belirlenebilir. Diş hekiminin deneyimi ile birlikte biyometrik parametrelerin ölçümü, diş hekiminin, diş anksiyetesi olan hastaların tedavisinde tercih edilen prosedürler ve yaklaşımlar hakkında kararlar almasını sağlayabilir.

Introduction

Dental anxiety is an emotional state during which various emotional/motivational changes (concern, fear, stress, and/or excitement) are observed. The effects of this anxiety can impact both the patient and the dentist. The majority of patients experience significant general stress due to previous experiences or environmental factors. Patients with severe anxiety cannot usually suppress their fear, and their emotional reactions, such as vomiting, crying, screaming, etc., may interfere with the surgical intervention. Therefore, general anaesthesia and/or sedation may be necessary. A detailed examination of the patient and the selection of an appropriate approach may help prevent the use of general anaesthesia and sedation; that is, it may allow for the intervention to be conducted under routine clinical conditions. Unnecessary and high-risk procedures are thus avoided, and an atmosphere of mutual trust is established between patient and dentist (1-4).

Electrodermal activity (EDA) known as galvanic skin response (GSR) enables the measurement of unconscious behaviours that cannot be voluntarily controlled. The skin is the largest organ of the body, and it reacts to all cognitive and emotional stimuli through an unconscious system controlled by the autonomous sympathetic nervous system. These reactions can be observed through changes in skin conductance, making the GSR technique an ideal biometric data collection tool for the investigation of emotional/motivational changes (5).

Compared to studies in the literature that are generally focused on the causes of anxiety, this study has a unique mixed-method design and interdisciplinary approach. The biometric recording of patients' anxiety characteristics and the comparison of the results with other reliable and validated anxiety scales are distinctive features of this study. In addition, this study represents a comprehensive attempt to improve data reliability through correct interpretation of the objective numeric data obtained from the interventions and the detailed interviews carried out after the interventions. The objective numeric assessment of the predictive data can contribute to developing a suitable dental treatment approach for patients with dental anxiety.

In this study, the following questions were explored:

- Can surgery for impacted tooth be considered as having different anxiety stages? Which stages specifically (pre-surgery session, oral surgery session, or post-surgery session) have an effect on patients' anxiety level?
- Are the results of dental anxiety scales (DAS) consistent for every patient in the clinical practice?
- Does the patient-dentist interaction affect the anxiety of the patient during surgery?

The main objective of this study is to determine and define the experience and stages of dental anxiety for oral and maxillofacial surgery patients, using real-time biometric data tools. In addition, this study addresses appropriate management of the patient-dentist interaction.

Materials and Methods

The study sample consisted of patients who were older than 18 years, had no systemic disorders, were not under psychiatric treatment and had applied to the Department of Oral and Maxillofacial Surgery in the Faculty of Dentistry at Aydın Adnan Menderes University. Patients who received medical treatment and who had a local pathological condition at the site of the impacted tooth were excluded from the study. The study group was limited to optimise the surgical conditions and to standardise the interventions for the biometric analysis of patients' dental anxiety levels. We included patients who had impacted teeth with vertical and mucosal retention in the mandible according to the Pell-Gregory classification. All patients were informed about the objective of the study and the details of the intervention, and

only patients who had given their written consent were included in the study. This study followed the Declaration of Helsinki regarding medical protocol and ethics, and the regional Ethical Review Board of Aydın Adnan Menderes University Faculty of Dentistry, approved the study (protocol no: ADÜDHF 2019/066, date: 17.04.2019).

In this study, patient-dentist interaction was divided into three sessions: the pre-surgery session, the oral surgery session, and the post-surgery session. The study procedures are shown in detail in Table 1. In this study, our approach was interdisciplinary and involved of the perspectives of both dentistry and communication sciences.

Pre-surgery Session

The pre-surgery session refers to the period before the patient was taken into the operating room. In this period, the first interview with the patient and the Modified Dental Anxiety scale (MDAS) survey were conducted. Also, participatory action research (PAR) was started to determine the overall anxiety level of the patient.

Oral Surgery Session

All surgical interventions were carried out in a single-unit treatment room with standardised illumination, and patients were situated in the room individually. The patients were isolated from stimuli except for the surgical intervention so that only the anxiety related to the surgical stages could be examined. The surgical intervention was divided into three phases: the pre-operative phase (pre-op), the operative phase (op) and the post-operative phase (post-op). As shown in Table 1, each phase was divided into subphases. Biometric data was collected using GSR in all subphases of the oral surgery session, while observation was carried out with PAR at the same time.

Post-surgery Session

The post-surgery session refers to the period following the surgical intervention, when the embedded third molar tooth extraction was completed. In this session, the state-trait anxiety inventory (STAI) was administered to determine the patient's anxiety status; in addition, a general analysis of the patient's anxiety status using PAR and an in-depth interview were conducted, and a cross-check of the STAI was carried out.

Modified Dental Anxiety Scale

The DAS, which was developed by Corah (6), is one of the oldest and most frequently used scales to measure dental anxiety. Humphris et al. (7) improved certain deficiencies of the DAS and developed the MDAS. The validity and reliability of the Turkish version of this modified scale, which enables a more accurate assessment of dental anxiety, was established (8). MDAS uses a 5-point Likert scale (1= not anxious, 2= slightly anxious, 3= fairly anxious, 4= very anxious, and 5= extremely anxious), the total score is between 5 and 25 points.

State-trait Anxiety Inventory

The (STAI-I, STAI-II) was developed by Spielberg et al. (9). Öner and Le Compte (10) adapted it to the

Table 1. Methods and stages of the procedure

Pre-surgery session	Oral surgery session			Post-surgery session
	Pre-operative phase	Operative phase	Post-operative phase	
Modified Dental Anxiety scale	P1. Unit preparation P2. Surgical field preparation P3. Surgeon preparation	P4. Local anaesthesia P5. Waiting anaesthesia P6. Incision P7. Tooth extraction P8. Bleeding control P9. Suturation P10. End of extraction	P11. Surgery information P12. Post-operative information P13. End of surgery	State and trait anxiety inventory
-	Galvanic skin response (SCL) & Heart rate (HR-bpm)	Galvanic skin response (SCL) & (HR-bpm)	Galvanic skin response (SCL) & (HR-bpm)	-
PAR	PAR	PAR	PAR	PAR In-depth interview

SCL: Skin conductance level, PAR: Participatory action research, HR: Heart rate

Turkish language and conducted reliability and validity tests for the Turkish version. This inventory has two 20-item scales. The anxiety state scale has a 4-point Likert scale, in which 1= not at all, 2= somewhat, 3= moderately so and 4= very much so. The trait anxiety scale is also based on a 4-point Likert scale that assesses the frequency of impressions, thoughts and behaviours, in which 1= almost never, 2= sometimes, 3= often and 4= almost always (11,12).

Galvanic Skin Response

The GSR device, which measures EDA, was designed for maximum patient comfort. It has only a few connection electrodes and can be easily be applied to patients to collect biometric data. Data were recorded with a Shimmer GSR+ device and analysed simultaneously with the Consensys PRO 1.5.0 software package (13). The Shimmer GSR+ equipment has three channels generating simultaneous feedback. Two of these channels record electrodermal skin conductance level (SCL) signals through the hand electrodes connected to the first and middle fingers, and the third channel collects cardiac volume data from an infrared sensor attached to the left earlobe and converts this data into heart rate (HR) data with the help of a software algorithm. We began recording the SCL of patients, which reveals changes in patients' emotions, as soon as they sat in the dental chair for the tooth extraction procedure (Figure 1).

"Motivational" is the adjective used in the GSR literature to refer to a patient's emotional state (anxiety, fear, excitement, concern, etc.). A change of emotion is described as a change of motivational status. Change is measured by an electrodermal data collection method. The MDAS and the STAI are also administered to identify a change in anxiety state, comprising a mixed method approach. Thus, as can be seen in the research, it is possible to identify in which stages a patient's emotional/motivational state variable changes to anxiety.

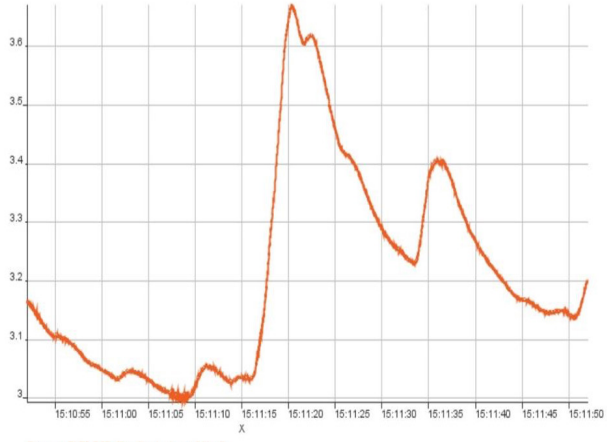

Figure 1. Galvanic skin response skin conductance response measurement of a patient during the oral surgery

In-depth Interview

According to the mixed-method research design, both quantitative and qualitative data were obtained from the participants. Observation and in-depth interview techniques were implemented to collect the qualitative data. Observation is not only a fundamental data collection method within traditional field research but is also one of the key elements of user research in the context of human-computer interaction. On the other hand, in-depth interviews are based on mutual verbal communication, during which the investigator can create a conversational atmosphere using predetermined topic areas to obtain in-depth information about the behaviours, opinions, emotions and beliefs of participants (14). This method was used as an additional tool to differentiate anxiety from other moods. In our study, in-depth interviews were carried out in the post-surgical session to support the detection of the patient's anxiety status using GSR. Through in-depth interviews, it is also possible to find and clarify which emotional changes in the patient's status of surgical operations correspond to.

Participatory Action Research

PAR is a technique in which the researcher is involved in the field as a participant, plays an active role in the actions of the research and conducts processes in the name of observing the data. In this method, it is possible to adapt the researcher to the field with multiple roles (15). This method was first coined action research by Lewin (16) (1951). In this method, the investigator can play more than one role in the research field. In our study, the dentist who performed the surgical operation was also a participant observation researcher. In addition to performing the embedded tooth operation, the dentist monitored the patient's GSR data and observed the patient's general emotional/motivational status. The other researcher checked and recorded the GSR data and supervised the flow of the mixed-method approach, observing the condition of the patient and the procedure carried out by the dentist.

Statistical Analysis

The G-Power v3.1.9.2 software package was used to calculate the sample size. Relevant studies in the literature were explored, and we referred to the study conducted by Najafpour et al. (17), which was similar to our study. The effect size, which was obtained with the study data, was too high (0.905), so we referred to an effect size of 0.50; consequently, the sample size was calculated to be 38. The type 1 error rate was set to 0.05, and the power of the study was set to 0.95 by G-Power analysis. The Lilliefors-corrected Kolmogorov-Smirnov test was used for the normal distribution analysis. As some data were not normally distributed, we used non-parametric tests for the analysis. We used the Spearman's correlation test to determine the direction and degree of the relationship between the variables and the Friedman test (two-way analysis of variance by ranks) to investigate the differences between the pre-op, op and post-op data. The Bonferroni test was used as a post-hoc test for multiple comparisons according to the results of the Friedman test. The chi-square test was used to compare patients' anxiety levels before and after the oral surgery. The two-way repeated-measures ANOVA was used to analyse the effect of variables such as age, gender, duration, MDAS and STAI on SCL and pulse values. Considering the ANOVA results, the Bonferroni test was used to perform paired comparisons.

Results

A total of 38 patients were included in the study with a mean age of 24.8 years (18-39 years). Fifteen were men (39.5%), and 23 were women (60.5%). According to the STAI, 10 participants (26%) experienced a high level of trait anxiety and 10 participants (26%) experienced a moderate level of trait anxiety, while 18 participants (48%) had no or only mild anxiety. Regarding patients' STAI scores for state anxiety, 27 participants (71%) had no or only mild state anxiety during the dental intervention, three participants (8%) had moderate state anxiety, and eight participants (21%) had a high level of state anxiety during the dental intervention. An analysis of patients' scores on the STAI state and trait scales using Spearman's Correlation test showed a positive and moderate correlation between these two scores ($p<0.001$). These findings indicate that patients' anxiety level increased significantly during the dental intervention with an increase in the general level of anxiety; in addition, individuals with general anxiety experienced more anxiety during the dental intervention (Table 2).

A two-way repeated measures ANOVA was used for each variable as well as HR and GSR values to analyse the relationship between the GSR and HR values and the independent variables. According to the patients' MDAS scores, 24 of the participants (63.2%) had no anxiety (MDAS<15), and 14 (36.8%) had anxiety (MDAS>15). Although there was no statistically significant correlation between patients' MDAS scores and the change in their GSR values ($p=0.464$), we determined a statistically significant correlation between MDAS scores and HR values ($p=0.008$). We also found a statistically significant correlation between age and GSR values ($p=0.011$). However, there was no statistically significant correlation between age and HR values ($p=0.231$). Regarding the gender of the participants, there was no statistically significant correlation between gender and GSR values ($p=0.732$), but there was a statistically significant correlation between gender and HR values ($p=0.002$). According to the findings, HR changed more among women compared to men. We did not detect any statistically significant correlation between the STAI scores and the changes in GSR and HR values ($p>0.05$) (Table 3).

As described above, in this study, the patient-dentist interaction was divided into three sessions-pre-surgery, oral surgery, and post-surgery. Oral surgery

Table 2. Scores of MDAS, STAI state and Trait scales

	MDAS		STAI state			STAI trait		
Score	**No (<15)**	**Yes (>15)**	**1st level (20-37)**	**2nd level (38-44)**	**3rd level (45-80)**	**1st level (20-37)**	**2nd level (38-44)**	**3rd level (45-80)**
Frequency (n)	24	14	27	3	8	18	10	10
%	63.2	36.8	71.1	7.9	21.1	47.4	26.3	26.3

MDAS: Modify Dental Anxiety scale, STAI: State-trait anxiety inventory

session was divided into three phase and each phase was divided into three, seven, and three sub-phases respectively. The mean values for patients during the oral surgery session are shown in Figure 2. While there was a significant difference between the GSR values in the pre-op phase ($p<0.001$), no significant differences were found between the changes in the HR values ($p=0.544$). According to the paired comparison of the pre-op GSR values, there was a statistically significant correlation between unit preparation (P1) and surgeon preparation (P3) ($p<0.001$). However, we did not determine a statistically significant correlation between P1 and surgical field preparation. We noticed that P3 was responsible for the significant difference. The last level of the pre-op phase (P3) had a statistically high value compared to the other levels (Figure 3).

In the op, which is the second sub-phase of the oral surgery session, the changes in the GSR and HR values were compared. According to the results of the Friedman test, there was a statistically significant difference between the mean values of op GSR and op HR ($p<0.001$). The changes in GSR and HR values during the sub-phases of the oral surgery are presented in Figure 4.

The results of the Friedman test revealed a statistically significant difference between the post-op GSR and HR values ($p<0.001$). The surgery (P11) values were significantly higher than the end of surgery (P13) values, and there was a statistically

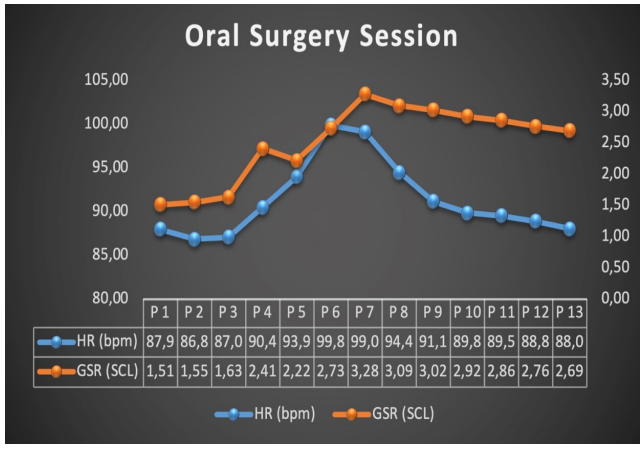

Figure 2. Mean values of the oral surgery session and the reaction of each level

GSR: Galvanic skin response, HR: Heart rate, SCL: Skin conductance level

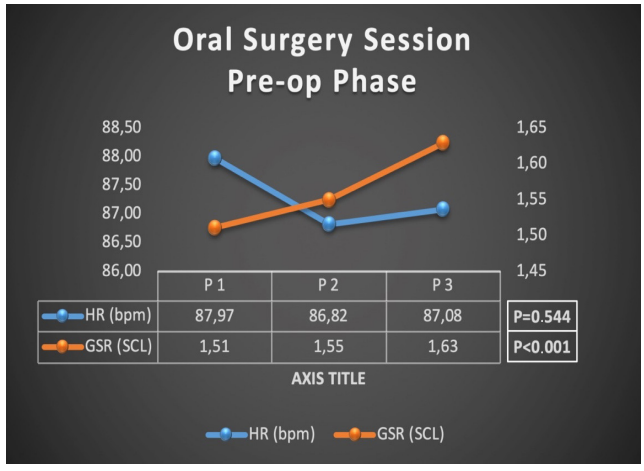

Figure 3. Mean values of the pre-operative phase of the oral surgery session and the reaction of each level

GSR: Galvanic skin response, HR: Heart rate, SCL: Skin conductance level, Pre-op phase: Pre-operative phase

Table 3. Tests of between-subjects effects of each parameters

		Mean square	F	p	Partial eta squared
MDAS	GSR	8,560	0,548	0.464	0,015
	HR	11749,821	7,958	0.008	0,181
Age	GSR	157,266	4,308	0.011	0,275
	HR	7602,440	1,504	0.231	0,117
Sex	GSR	1,880	0,119	0.732	0,003
	HR	15555,460	11,347	0.002	0,240
STAI	GSR	36,157	2,538	0.093	0,127
	HR	4608,136	2,896	0.069	0,142
Educational status	GSR	16,624	1,087	0.379	0,116
	HR	625,845	0,331	0.855	0,039

STAI: State-trait anxiety inventory, MDAS: Modify Dental Anxiety scale, HR: Heart rate, GSR: Galvanic skin response

significant difference between information P11 and P13 (p<0.001) (Figure 5).

Discussion

It is well known that anxiety and fear are common experienced by patients during dental treatments, and they create a disadvantageous stress for patients. Ayaz and Varol (3) reported that the concepts of anxiety and fear are often intermixed and used interchangeably; however, the meaning and content of these emotions is different. Fear is defined as a subjective emotion, which emerges as a reaction against a known danger. On the other hand, anxiety is defined as a state of concern and uneasiness in the presence of an unknown danger or threat (2,3,18).

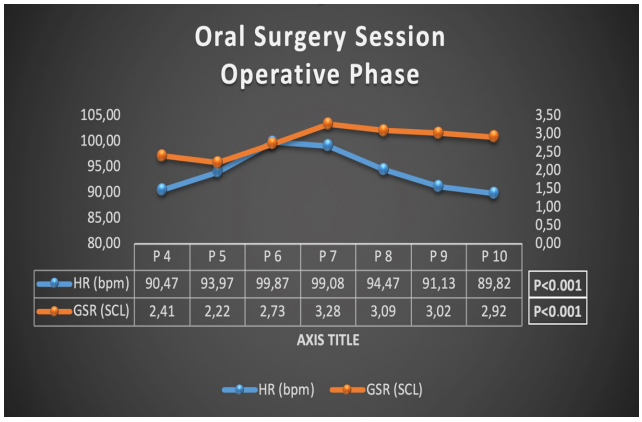

Figure 4. Mean values of the operative phase of the oral surgery session and the reaction of each level

GSR: Galvanic skin response, HR: Heart rate, SCL: Skin conductance level

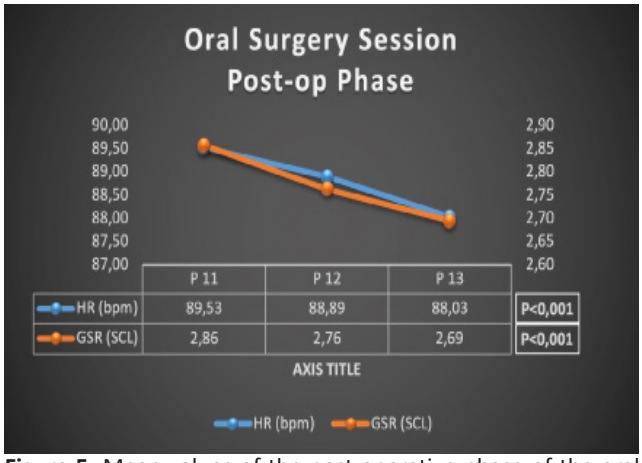

Figure 5. Mean values of the post-operative phase of the oral surgery session and the reaction of each level

GSR: Galvanic skin response, HR: Heart rate, SCL: Skin conductance level, Post-op phase: Post-operative phase

Bayındır et al. (19) defined dental anxiety as a high level of uneasiness, which develops as a result of fear and concern during the dental treatment and cannot be openly expressed. Bulut et al. (11) identified the factors that cause the emergence of anxiety, such as long and exhausting therapeutic procedures, sounds created by the equipment, previous unpleasant experiences and social experiences.

Several scales have been developed and implemented in collaborations between different disciplines to define and assess dental anxiety. Several studies focused particularly on the definition and understanding of dental anxiety (6,7,11,20-24). Ay et al. (2) conducted a study to define and treat dental anxiety; they suggested that the most important factor was the necessity to focus on the cause of fear and anxiety. As a result of the individual characteristics of dental anxiety, it is important to understand the specific and individual relationship of anxiety with the distinct phases of the procedure to elucidate the definition, clinical presentation and prevention of dental anxiety.

The biometric data collection method enables the mathematical definition of anxiety levels (25,26). Like other autonomous processes (e.g. body temperature, heart rhythm, blood pressure, etc.), sweating cannot be controlled consciously. Skin conductance is also affected by this autonomous sweating process and can be tracked with a GSR. The autonomous sympathetic system, which can trigger a fight-or-flight reaction depending on the stimuli, functions as an automatic warning mechanism with the help of the centres managed unconsciously by the sympathetic nervous system. Since 1972, several research articles have been published that focused on the reactions of the sympathetic nervous system, and they have recorded these reactions using the GSR method. Therefore, GSR has become one of the most reliable measurement techniques in the technical and scientific literature (27). Our emotional stimulation level changes in response to the environment. If something frightening, threatening, or amusing occurs, the emotional response increases the activity of the eccrine sweat glands. Skin conductance is not under conscious control. Instead, it is autonomously modulated by the sympathetic activity, which shapes human behaviour along with cognitive and emotional reactions. Therefore, skin conductance provides

a direct perspective on autonomous emotional regulation (28). Research has confirmed that this reaction is related to emotional stimulation (5,28,29). It should be noted that both positive ("happy" or "cheerful") and negative ("threatening" or "sad") stimuli increase excitability and skin conductance. Therefore, the GSR signal represents the intensity, not the type of emotion.

Only a few studies have focused on the implementation of GSR in dentistry. Caprara et al. (25) conducted a study on the objective measurement of dental anxiety using GSR; they reported that their objective was to determine whether the weak electric current caused by anxiety could be objectively measured. In the study, three different measurements were performed: first, a standard anxiety survey was administered; second, the galvanic skin conductance was measured; finally, false replies to three questions were recorded (25). Najafpour et al. (17) conducted a study on 151 paediatric patients and evaluated GSR measurements. They stated that GSR provided reliable and realistic data for determining dental anxiety. In their study, Casap et al. (30) investigated the effects of informed patient consent on stress levels during third molar extraction with the help of the electrodermal skin response technique.

In the present study, STAI and MDAS scales, which have up-to-date literature support, were used, and GSR was added to the study to collect biometric data. The emotions and thoughts of patients can change over the course of a dental procedure, and scales cannot always capture data with a uniform accuracy. The most significant disadvantage of the scales is their subjectivity. With the help of the objective data collected with the biometric method, the accuracy of existing anxiety scales can be tested. In this study, we had the opportunity to compare MDAS and STAI data with the biometric data. It was expected that the GSR and HR values would increase when the patient experienced continuous anxiety according to the STAI scale (STAI-2, state anxiety) and the MDAS score was above the threshold (>15). We were not able to demonstrate any effect of anxiety determined with MDAS and STAI on the changes in the SCL values.

In this study, we tried to find out which emotional/motivational changes were experienced during which stages of the dental intervention. In addition, these mood changes became distinguishable as fear, concern, or anxiety and, thus, showed how the patient-dentist interaction should be during the anaesthesia and extraction and in the following stages as well as demonstrating that appropriate communication was needed. It was expected that different emotional/motivational factors would underlie psychosomatic and anxious reactions during the key stages of the oral surgery and that these would be reflected by the biometric data.

Each phase within the three sessions of the patient-dentist interaction was divided into levels according to the implemented processes. We evaluated the changes within the timeframe of each phase/level and investigated whether they affected the level of anxiety in patients. Data in the pre-op phase tended to anxiety increase gradually. This increase may be interpreted as an increase in stress as the time for the oral surgery came closer. The difference between the GSR and HR values and the elapsed time during the op confirms that the level of anxiety increased with the prolongation of the surgery, peaked at a certain time during the tooth extraction (P7), and continued at a high level; then it started to decline at the end of the surgery (P10). The decline of the anxiety level with the progress of the surgery may reflect the patient's emotions and thoughts related to the establishment of trust with the dentist, getting used to the environment, and the completion of the surgery. The decline in the GSR and HR values in the post-op session may be interpreted as the level of anxiety declining gradually after the completion of the surgery. These findings were supported by both values. The in-depth interviews confirmed these findings. It was observed that patients started to feel anxiety during the application of the anaesthesia and suffered from thoughts such as "What is going to happen to me?", and they experienced curiosity and anxiety again towards the end of the intervention.

In the pre-clinic study, the patients who did not show any significant numerical changes in the emotional/motivational variables according to the biometric data were identified, and these patients were considered to be the placebo group (15). It was reported that the psychosomatic reactions of patients could be manipulated, and the level of anxiety could be decreased with the appropriate approach to the patient on the part of the dentist (31). It was observed that the patient group which explained as placebo

patient before was large, and that patients who demanded sedation and/or general anaesthesia could not be managed properly by clinically inexperienced surgeons; thus, the need for anaesthesia and the related risk factors increased. The psychosomatic mood changes in the placebo patients, which until now could only be diagnosed by an experienced dentist, became detectable with biometric data collection.

It was observed that certain words used by the surgeon during the operation had a negative impact on the psychosomatic state of the patients. These words, known as triggering words, may cause severe anxiety. Therefore, it was emphasized that the operation should be managed by the dentist with carefully selected communication tools.

Conclusion

It was noticed that patients' emotional/motivational changes during the phases of the operation could be identified using the analyses of their biometric data. The simultaneous measurement of biometric parameters may, in tandem with the dentist's experience, enable the dentist to decide during the operation which procedures and approaches should be used with patients with dental anxiety. Regarding oral surgical interventions, an important step was taken toward the use of minimal surgical approaches instead of the use of additional sedation and/or general anaesthesia with the use of GSR and its components. Furthermore, we believe that this approach will also contribute to increasing patients' trust and interaction with the dentist. In future studies, the emotional/motivational findings during the stages of oral surgery can be investigated, and procedure packages based on the patient-dentist interaction can be implemented to determine a suitable surgical approach for patients with dental anxiety. Moreover, further studies are required to investigate the integration of biometric data collection devices into dental units so that dentists have the possibility of instantly using current data to adjust their approach to patients with dental anxiety.

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Ethics

Ethics Committee Approval: This study followed the Declaration of Helsinki regarding medical protocol and ethics, and the regional Ethical Review Board of Aydın Adnan Menderes University Faculty of Dentistry, approved the study (protocol no: ADÜDHF 2019/066, date: 17.04.2019).

Informed Consent: All patients were informed about the objective of the study and the details of the intervention, and only patients who had given their written consent were included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.O.Ş., B.A.A., Design: H.O.Ş., B.A.A., Data Collection or Processing: H.O.Ş., B.A.A., Analysis or Interpretation: H.O.Ş., B.A.A., Literature Search: H.O.Ş., B.A.A., Writing: H.O.Ş., B.A.A.

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

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Original Article / Özgün Araştırma

Percutaneous Endoscopic Gastrostomy Experience in A Tertiary Intensive Care Unit

Üçüncü Basamak Yoğun Bakımında Perkütan Endoskopik Gastrostomi Deneyimlerimiz

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Abstract

Objective: Percutaneous endoscopic gastrostomy (PEG) is a procedure performed for nutrition in patients whose gastrointestinal system functions are impaired. This study aimed to evaluate patients who were treated in our clinic and underwent PEG.

Materials and Methods: Patients older than 18 years who underwent PEG between November 2013 and November 2015 were studied. Patient follow-up forms and hospital electronic records were analysed retrospectively.

Results: Overall, 117 patients were enrolled, including 47 (40%) male patients. The mean Acute Physiology and Chronic Health Evaluation II score was 20±8; mean age, 72±15 years; mean length of stay, 43±42 days and mean procedure day, 14±5 days. About 35% of patients had dementia, 23.9% had malignancy and 22.3% had cerebrovascular disease. The total complication rate was 17%.

Conclusion: PEG is a safe procedure and provides patient comfort while maintaining enteral nutrition. Therefore, it is an effective method in feeding patients who cannot be fed orally in the long term.

Keywords
Enteral nutrition, gastrostomy, percutaneous endoscopic gastrostomy, intensive care

Anahtar Kelimeler
Enteral nutrisyon, gastrostomi, perkütan endoskopik gastrostomi, yoğun bakım

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Öz

Amaç: Perkütan endoskopik gastrostomi (PEG), gastrointestinal sistem fonksiyonlarını sürdüren hastalarda beslenme için kullanılan yöntemlerden biridir. Bu çalışmada amacımız, kliniğimizde tedavi edilen ve PEG işlemi uygulanan hastaların değerlendirilmesidir.

Gereç ve Yöntemler: Kasım 2013 ile Kasım 2015 arasında PEG prosedürü uygulanan 18 yaşından büyük hastalar çalışmaya dahil edildi. Hastaların takip formları ve hastane elektronik kayıtları retroskopik olarak incelendi.

Bulgular: Çalışmaya 117 hasta dahil edildi, hastaların 47'si (%40) erkekti. Ortalama Akut Fizyoloji ve Kronik Sağlık Değerlendirme II (APACHE II) skoru 20±8, ortalama yaş 72±15 yıl, ortalama yoğun bakım yatış süresi 43±42 gün ve ortalama işlem süresi 14±5 gündü. Hastaların %35'i demans, %23,9'u malignite, %22,3'ü serebrovasküler hastalık tanısı ile yoğun bakımda takip edilmekteydi. Toplam komplikasyon oranı %17'ydi.

Sonuç: PEG güvenli bir işlemdir, enteral beslenme fonksiyonlarını sürdüren hastalarda konfor sağlar. Uzun vadede ağızdan beslenemeyen hastaların beslenmesinde etkili bir yöntem olduğunu düşünüyoruz.

Introduction

Percutaneous endoscopic gastrostomy (PEG) is one of the methods used for nutrition in patients whose gastrointestinal system functions are maintained. It was first described in 1980 by Gauderer et al. (1). Nutrition with gastrostomy tube provides mucosal integrity, preserves normal flora and protects intestinal immunity (2). The advantageous aspects are that the procedure can be performed outside the operating room, has a short procedure time and low cost (3). Main indications are neurological diseases, psycho-mental retardation, cancers, unconscious conditions, frequent aspiration pneumonia, burns and congenital anomalies (4).

PEG should be evaluated according to the needs, preferences, diagnosis and life expectancy of the patient. The aim is not only to improve the survival and nutritional status of the patient, but also to improve the quality of life (5). Major complications are aspiration pneumonia, bleeding, necrotizing fasciitis and metastasis. Wound infection, PEG dislocation, tube obstruction, pneumoperitoneum, gastric outlet obstruction and peritonitis are minor complications (4).

Our aim in this study is to evaluate the patients who are treated in our clinic and underwent PEG procedure.

Materials and Methods

After obtaining the ethics committee approval (Ankara Numune Training and Research Hospital Clinical Research Ethics Committee decision no: 659/2015, date: 25.11.2015) our retrospective study was conducted in Ankara Numune Training and Research Hospital general tertiary intensive care unit between November 2013 and November 2015.

Patients older than 18 years old who underwent PEG procedure were included. One hundred seventeen patients were included in the study. Patient follow-up forms and hospital electronic records were analyzed retrospectively. Since our study was planned retrospectively, consent form was not obtained from the patients. In our unit, PEG procedure was performed in the endoscopy laboratory, and it was applied at the bedside for patients who cannot be transported. Enteral feeding was stopped 12 hours before the procedure and parenteral nutrition was started. Prophylactic antibiotherapy was not administered to patients who did not receive any antibiotherapy due to their treatment. During the procedure, sedo-anaesthesia was applied by a staff anesthesiologist. Enteral feeding was started with a low dose at the 8th hour after the procedure and the target dose was reached by increasing the dose every eight hours. A commercially available 18-Fr endoscopic gastrostomy set was used. By a special nutrition nurse care training was given to the relatives of the discharged patients.

Statistical Analysis

SPSS 22.0 for Windows was used for statistical data. Qualitative data were expressed as numbers and percentages, quantitative data were expressed as standard deviation.

Results

One hundred and seventeen patients were included in the study. The procedure was performed on 113 patients in the endoscopy laboratory. Four patients who could not be transported for gastrostomy, procedure performed at the bedside. Forty seven of the patients were male (40%). The mean Acute Physiology and Chronic Health Evaluation II score was 20±8, the mean age was 72±15 years, the mean lenght of stay was 43±42 days, and the mean PEG opening day was 14±5 days. PEG indications are given in Table 1.

The discharge types of the patients are given in Table 2.

The ventilation types of the patients on the day the procedure is shown in Table 3.

Complications seen after PEG procedure are presented in Table 4.

Table 1. Percutaneous endoscopic gastrostomy indications

	n	%
Dementia	41	35.0
Malignancy	28	23.9
Myopathy	5	4.3
Parkinson disease	7	6.0
Cerebrovascular disease	26	22.2
Intracranial hemorrage	10	8.5

Table 2. Types of discharge		
	n	%
Exitus	27	23.1
Transfer to palliative care	52	44.4
Discharge	29	24.8
Transfer to lesser degree intensive care unit	9	7.7

Table 3. Types of ventilation		
	n	%
Tracheotomy	70	59.8
Spontaneous ventilation	45	38.5
Tracheal intubation	2	1.7

Table 4. Complications		
	n	%
Infection	4	3.4
Hemorrage	3	2.5
Catheter leakage	8	6.8
Blockage	5	4.2
Total	20	17

Discussion

The superiority of percutaneous gastrostomy over conventional gastrostomy for artificial enteral nutrition has been reported in previous studies (6). With PEG, absence of mucosal atrophy and reduction of bacterial translocation, which are the advantages of enteral feeding is ensured, the integrity of the gastrointestinal system is preserved and the risk of infection is reduced (7).

In our study, we found that 35% of the patients had dementia, 22.2% had cerebrovascular events and 8.5% had intracerebral bleeding. Löser et al. (8) reported intracerebral hemorrhage 6.2% and cerebrovascular events 12.4% in their study covering a four-year period. Chang et al. (9) reported that neurological disorders were 46%, esophageal damage 39.2%, and head and neck tumors 14.4%. It is clear that these rates vary according to the characteristics of the centers where the research was conducted. We think that dementia patients are higher due to the presence of intensive care for neurology in our center and less head and neck surgeries.

The average PEG procedure day was 14±5 days. It is recommended to provide an alternative enteral route for patients who unable to feed for a long time (10). Compared with nasoenteric nutrition, PEG has less risk of irritation, ulcer, bleeding, esophageal reflux and aspiration pneumonia (11). PEG is recommended for patients who are fed nasoenteric for 2-3 weeks and have medium-high malnutrition risk (4). In our center, patients who cannot be fed orally and whose enteral pathway are intact, nasoenteral route is provided and nutrition is started after admission. PEG is planned for patients who are fed nasoenterally for 12-14 days. We think that our average PEG procedure day is compatible with the recommended period in the literature.

In our study, we found that mortality was 23.1% in this patient group. The average length of stay was 43 days. Different mortality rates have been reported in various patient groups. Golestanian et al. (12) evaluated 8,185 patients with acute stroke and reported a 30-day mortality of 21% and a mean length of stay of 7.3±6.1 days. In his study by Oud (13), 276,056 elderly and dementia patients were retrospectively reviewed and the mean length of stay was reported as 7 days and mortality as 12%. We think that the length of stay and mortality rates are high due to the fact that the end-of-life decision cannot be made legally in our country, there is not enough palliative care and long-term intensive care bed. We previously reported that the tracheostomy procedure of geriatric patients was delayed due to the reluctance of their relatives and the average length of stay was prolonged (14). Long hospitalizations are also seen because the relatives of PEG patients do not allow discharge.

The fact that 59.8% of our patients had tracheostomy indicates that these patients are long-term intensive care patients.

No major complications were observed in any of our patients, and minor complications developed. Our complication rate was found to be 17%. Ozguc et al. (15) 12.2%; Kahramanoğlu Aksoy et al. (16) 15.9%; Löser et al. (8) 23%; Schneider et al. (17) 17%; reported complication rates. We found that our complication rate was compatible with the literature. None of our patients died due to PEG-related complications, and our patients died due to other reasons.

The weak points of our study are its retrospective nature and not evaluating long-term mortality.

Conclusion

PEG procedure, which has previously been proven to be superior to surgical gastrostomy, is safe, it is a method that provides patient comfort while maintaining enteral nutrition. We think that it is an effective method for feeding patients who cannot be fed orally in the long term.

Ethics

Ethics Committee Approval: This study was approved by the Ankara Numune Training and Research Hospital Clinical Research Ethics Committee (decision no: 659/2015, date: 25.11.2015).

Informed Consent: Since our study was planned retrospectively, consent form was not obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: P.Ö.Y., Design: P.Ö.Y., C.D., Supervision: C.D., Materials: P.Ö.Y., Data Collection or Processing: C.D., Analysis or Interpretation: C.D., Literature Search: C.D., P.Ö.Y., Critical Review: P.Ö.Y., Writing: C.D., P.Ö.Y.

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Original Article / Özgün Araştırma

Evaluation of Complications Associated with Surgically Assisted Rapid Maxillary Expansion in Cases with or Without Pterygomaxillary Disjunction

Pterygomaksiller Ayrılmanın Olduğu Ya Da Olmadığı Olgularda Cerrahi Destekli Hızlı Maksiller Genişletme ile İlişkili Komplikasyonların Değerlendirilmesi

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Keywords
SARME, surgery-assisted maxillary expansion complications, pterygomaxillary disjunction

Anahtar Kelimeler
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Abstract

Objective: Surgically assisted rapid maxillary expansion (SARME) is a widely used treatment method for the correction of transversal deficiencies of the maxilla. The gold standard treatment method among various surgical techniques has not been established. This retrospective study aimed to determine complications in SARME cases with and without pterygomaxillary disjunction and evaluate the differences between intraoperative and post-operative complications between the two groups.

Materials and Methods: We enrolled 38 patients (25 females and 13 males) who underwent SARME under general anaesthesia at Aydın Adnan Menderes University Faculty of Dentistry between January 2015 and January 2020 in this study. These patients were divided into the following two groups: Patients with pterygomaxillary disjunction group and patients without pterygomaxillary disjunction group. The intraoperative and post-operative complications were evaluated for both the groups.

Results: Technically, the pterygoid junction was broken in 17 of the 38 patients included in this study with SARME; however, it was intact in 21 patients. Intraoperative haemorrhage was observed in two patients in the group with pterygomaxillary disjunction and in one patient in the group without pterygomaxillary disjunction. Electrocauterisation was performed to control bleeding in both the groups. In the group with pterygomaxillary disjunction, post-operative hematoma was observed following intraoperative haemorrhage in two patients, post-operative asymmetric expansion in two patients and post-operative unilateral transient paraesthesia in one patient.

Conclusion: The most common complication was haemorrhage, which was more observed in the group with pterygomaxillary disjunction. However, asymmetric disjunction was also seen in the group with pterygomaxillary disjunction. Whereas, minor complications were observed in the group without pterygomaxillary disjunction. As a result, the surgical technique, where the pterygoid junction remained intact, has minimal risk for complications.

Öz

Amaç: Cerrahi destekli maksiller genişletme, maksillanın transversal yön yetersizliklerinin düzeltilmesinde yaygın olarak kullanılan bir tedavi yöntemidir. Yapılan çalışmalarda bu tedavi yönteminde kullanılan farklı cerrahi tekniklerle ilgili bir altın standart bulunamamıştır. Bu retrospektif çalışmanın amacı pterygomaksiller ayrılmanın gerçekleştiği ve gerçekleşmediği cerrahi destekli hızlı üst çene genişletme olgularında görülen komplikasyonları belirlemek ve iki grup arasındaki intraoperatif ve post-operatif komplikasyon farkını değerlendirmektir.

Gereç ve Yöntemler: Aydın Adnan Menderes Üniversitesi Diş Hekimliği Fakültesi'nde Ocak 2015-Ocak 2020 tarihleri arasında genel anestezi altında cerrahi destekli hızlı maksiller genişletme yapılmış tüm hastaların verileri retrospektif olarak taranmıştır. Dosyada verileri tam olan 38 adet hasta çalışmaya dahil edilmiştir. Bu hastalar pterygomaksiller ayrılma olan ve olmayan olarak iki gruba ayrılarak, bu iki grup için de intraoperatif ve post-operatif komplikasyonlar değerlendirilmiştir.

Bulgular: Çalışmaya dahil edilen 38 hastanın (25 kadın,13 erkek) 17'sinde cerrahi destekli maksiller genişletmede teknik olarak pterygoid bağlantı kırılmış, 21'inde ise pterygoid bağlantı kırılmamıştı. Pterygoid ayrılan grupta 2 hastada, pterygoid ayrılmayan grupta ise 1 hastada intraoperatif hemoraji geliştiği görüldü. Her iki grupta da kanama kontrolü için elektrokoterizasyon kullanılmıştı. Pterygoid ayrılan grupta 2 hastada intraoperatif hemorajiyi takiben postoperatif hematom, 2 hastada post-operatif asimetrik ekspansiyon ve 1 hastada post-operatif tek taraflı geçici parestezi görüldü.

Sonuç: En sık karşılaşılan komplikasyon hemorajiydi ve bu da pterygoid bağlantının ayrıldığı grupta daha sık gözlendi. Yine asimetrik ayrılma da pterygoid bağlantının ayrıldığı grupta görüldü. Pterygoid bağlantının ayrılmadığı grupta minör komplikasyonlar gözlendi. Sonuç olarak pterygoid bağlantının kırılmadığı cerrahi teknik komplikasyon açısından daha az risklidir.

Introduction

Maxillary expansion is an orthodontic treatment that is widely used to correct transversal deficiencies maxilla (1). When this expansion method is applied in a patient with skeletal maturity; undesirable effects such as lateral tipping of posterior teeth, extrusion, periodontal membrane compression, bending of the alveolar bone, buccal cortex fenestration, palatal tissue necrosis, failure to open the midpalatal suture, pain and instability in maxillary expansion (2). As attempts to orthopedically change the transversal size of the maxilla with advancing age cause more complications, surgical procedures have been recommended to facilitate correction of transversal discrepancies.

The purpose of surgically assisted rapid maxillary expansion (SARME); is to provide skeletal expansion instead of dental enlargement and to minimize dental tipping by separating the midpalatal and lateral maxillary sutures (3). SARME; is preferred in patients with skeletal maturity and having maxillary transversal insufficiency more than 5 mm.

In early studies, midpalatal suture was defined as the area of greatest resistance to maxillary expansion (4-6). It is advocated in some publications that it is required to avoid pterygomaxillary disjunction (PMD) to make the surgery less invasive (7). However, subsequent reports highlight that the zygomatic buttress and pterygomaxillary junction are areas of critical resistance (2,8-10). However, depending on the area where maxilla expansion is desired, it may be necessary to disconnect the maxilla from the pterygoid plates during the SARME operation. When osteotomy is not performed in this area, which is one of the most important points of resistance, the posterior nasal spina acts as a rotation center due to the resistance in the pterygomaxillary junction and while the enlargement is seen more in the anterior of the maxilla, and less in the posterior (11).

Although SARME is considered a safe and simple procedure, its complication rate remains uncertain. Researches published in the literature report variable results along with complications in 1% to 50% of the cases (3,12,13). Researches that found high complication rates divided the complications into minor and major. Major complications are those associated with high morbidity, risk of death or permanent sequellae. Minor complications do not cause sequellae and require simple outpatient treatment (3,13-16). In addition to surgical complications, some orthodontic complications such as asymmetric maxillary expansion or tooth extrusion are frequently identified (17-19).

Despite the application of new techniques, the incidence of complications and the types of complications associated with each technique remain uncertain. In this research, complications developed in SARME cases with and without PMD were determined, and the difference in complications during or after

surgery between cases with and without PMD was evaluated.

Materials and Methods

All patients, who underwent SARME surgery under General Anesthesia at Aydın Adnan Menderes University Faculty of Dentistry between January 2015 and January 2020, were retrospectively scanned. Ethical approval was obtained from Aydın Adnan Menderes University Faculty of Dentistry Clinical Research Ethics Committee (protocol no: 2020/01, date: 05.08.2020). The protocol was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki. All patients reviewed and signed written informed consent forms.

Thirty-eight patients, who met the inclusion criteria, were grouped as with and without PMD during corticotomy. The same surgical team used the same techniques in each group. The orthodontist cemented the fixed hyrax type expansion appliance 1-2 days before surgery. Inclusion criteria for this research; are the cases which have completed skeletal development, in which bilateral maxillary stenosis is greater than 5 mm, which has good oral hygiene and healthy periodontal tissue. The presence of one of the maxillary sinus diseases and those with previous maxillomandibular intervention were not included in the study. Intraoperative and post-operative 6-month complications were evaluated in the group with and without PMD. Complication data collected for each patient during and after surgery for 6 months in both groups were analyzed. Prediction variables include demographic parameters (age and gender).

Surgical Technique

A standard surgical technique applied under general anesthesia in the operating room was used in all cases. Local anesthesia was routinely applied for hemostasis before incision. A full-thickness maxillary vestibular incision was made bilaterally extending from the first molar mesial to the distal of the ipsilateral canine tooth and subperiosteal dissection was completed to show the maxilla from the piriform rim to the buttress. The flap is elevated atraumatically and minimally to prevent possible tissue necrosis in the anterior region of maxilla in the planned interdental osteotomy site (usually midline). Osteotomy in Le Fort I level was performed using a straight fissure drill. In addition, in the group where PMD occurs, pterydoid plates are disconnected with the help of osteotome. The Hyrax appliance was activated to see the independent movement of two segments of maxilla and later it was deactivated and the flap was repositioned and sutured.

Statistical Analysis

Statistical analysis was made by using Statistical Package for Social Sciences software package (for Windows 98, version 10.0; SPSS, Chicago, IL, USA). All data given were calculated by descriptive statistics method over numbers and percentages.

Results

Of the 38 patients included in the research, 25 of them were female and 13 of them were male. In 17 of 38 patients, SARME was done with PMD, and in 21 patients without PMD.

Considering the total number of patients included, the gender distribution was higher for women, with 65.78% female and 34.22% male.

Intraoperative hemorrhage was observed in 2 patients in the with PMD group and 1 patient in the without PMD group. Electrocauterization was used to control bleeding in both groups. In the with PMD group, post-operative hematoma was observed in 2 patients following intraoperative hemorrhage, post-operative asymmetric expansion in 2 patients, and post-operative unilateral transient paresthesia in 1 patient likewise. In the without PMD group, 1 patient developed epistaxis on the post-operative 1st day after intraoperative hemorrhage. No laceration, sinus infection, permanent nerve damage, dental or periodontal problems were encountered in any patient. When the complication reports were discussed individually, while the rate of complications in women was 18.18% in the with PMD group and 7.14% in the without PMD group, it is 33.33% in the with PMD group and 14.28 in the without PMD group. The post-operative follow-up period of these patients was 6 months.

When the patients were evaluated in terms of age, the age distribution was between 15-31, the average age was 19.68. For the with PMD group, while the mean age with complications was 24.25 and the mean age without complications was 21.07, as for the without PMD group, the mean age with complications was 21.5, and the mean age without complications was 17.55. By looking at both groups,

the average age was found to be higher in the groups with complications.

Discussion

Although SARME is a frequently used treatment in the treatment of transversal maxillary constriction, post-operative complications such as pain, bleeding, infection, sinusitis, dental and periodontal problems, palatal mucosa ulceration, asymmetric expansion, recurrence, aseptic necrosis, orbital complications can be seen, but there is not a clear information about the incidence of complications (3). It was reported that SARME had lower morbidity while being compared to other orthognathic surgical procedures (20). The development of a nasopalatine duct cyst, bilateral lingual anesthesia and orbital compartment syndrome, have also been reported among some unusual complications (2). There are also publications that mention complications related to expansion device (21).

PMD is still a controversial subject in the literature. Some authors support PMD by suggesting that the pterygomaxillary buttress creates an area of resistance in expansion and that without PMD increases the likelihood of erroneous expansion. However, another controversial issue is the increasing surgical complications when PMD is performed (16,22,23). There are also publications that mention making surgery non-invasive by avoiding PMD. The study is a multidisciplinary topic as it concerns both oral and maxillofacial surgeons and orthodontists.

Timms and Vero (4) reported in their research that those over 25 years of age are appropriate for SARME. While Mommaerts (24) is recommending non-surgical maxillary expansion in patients younger than 12 years of age, he suggested that corticotomy is essential to release points of resistance for those over 14 years of age. Epker and Wolford (25) suggest SARME in patients over the age of 16. Our research had findings compatible with these studies. The patients we applied SARME were between the ages of 15-31 and the average age was 19.68.

It is thought that PMD performed by using an osteotome can trigger post-operative vascular events. In cases of upper jaw fractures, other factors such as a pseudoaneurysm, a high-level pterygoid plate fracture, late wound infection, and injuries to the sphenopalatine and descending palatine arteries during advanced maxillary mobilization can trigger life-threatening hemorrhage. However, SARME causes much lower morbidity in particular compared to down fracture of the maxilla in Le Fort (14). In the large SARME case series by Politis (26) (376 patients), no life-threatening haemorrhage was noted. In this research, it was seen that post-operative hematoma developed following intraoperative hemorrhage in 2 patients in the with PMD group, and intraoperative hemorrhage developed in 1 patient in the without PMD group. Electrocauterization was used to control bleeding in both groups.

Epistaxis is a frequently reported complication as a possible result of surgical damage to soft tissues around the maxillary sinus and nasal cavity (12-14). When epistaxis develops, it is easily treated with compression and nasal buffering. Dergin et al. (12) when evaluating the complications after SARME retrospectively, they reported that 20% of all patients developed epistaxis. On the other hand, Mehra et al. (27) reported a life-threatening case of delayed epistaxis after SARME. In our research, an epistaxis developed in one patient (2.63%) in the without PMD group on the day following surgery. Hemostasis was achieved with an anterior nasal buffering. Since PMD was not performed in this patient, the probable cause of bleeding is traumatic osteotomy of the lateral nasal wall.

It was reported that changes in blood flow and damage to the branches of the maxillary nerve caused paresthesia in the infraorbital region and lips, and numbness in the teeth (13). Subjective changes in gingival numbness somatosensorial function, and cutaneous numbness in the face and palate have also been reported in the literature (28,29). One of the patients in the PMD group reported transient unilateral mild facial paresthesia possibly related to trauma to the infraorbital nerve by tissue retractors and temporary unilateral numbness of the gums. All the numbness ameliorated 6 months after the operation.

Asymmetric expansion seen after SARME; is the main complication whose prevalence has been reported in a wide variation from 3.4% to 18% (30-34). Asymmetrical or uneven expansion may be due to slow activation rate or PMD deficiency. Verlinden et al. (31) reported in their research that asymmetric expansion developed in 5 of the 73 cases and that all

cases with asymmetric expansion required additional surgery. Seitz et al. (32) reported in their study that asymmetric expansion was the most common surgical complication in a group of 22 patients. Koudstaal et al. (34,35) recorded asymmetric expansion in 2 of 46 patients and 4 out of 10 heads, and concluded that the potential problem was retention in the pterygomaxillary junction. They thought that although PMD was done, asymmetrical movement occurred in the maxillary segments as a result of the incomplete fracture on one side. In this research, asymmetric expansion was observed totally in 2 patients, 1 patient apiece in both groups. The same expansion appliance and the same RME protocol were applied to all patients evaluated in our research. As the slow expansion protocol was not applied, asymmetric expansion was not formed depending on the RME protocol. Carvalho et al. (36) suggested that the slow expansion protocol might be associated with asymmetric expansion complication due to early callus formation. Like other researchers, we think that the occurring of asymmetric expansion despite the PMD is due to the absence of complete disjunction on one side. (34,35). No extra surgery was applied on these patients. It was observed that dental transversal were compensated.

Conclusion

As a result of this research, the most common complication was hemorrhage and it was observed more frequently in the with PMD group. Major complications were not observed in any group. In conclusion, we think that surgical technique without pterygoid disjunction, is less risky in terms of complications. However, additional prospective and long-term follow-up researches with more cases are needed to clarify individual factors that may cause complications.

Ethics

Ethics Committee Approval: Ethical approval was obtained from Aydın Adnan Menderes University Faculty of Dentistry Clinical Research Ethics Committee (protocol no: 2020/01, date: 05.08.2020). The protocol was conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki.

Informed Consent: All patients reviewed and signed written informed consent forms.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.G., Design: B.G., Y.A.Ü., Supervision: B.G., Materials: M.N.A., Data Collection or Processing: M.N.A., Analysis or Interpretation: M.N.A., B.G., Literature Search: M.N.A., Critical Review: Y.A.Ü., Writing: B.G., Y.A.Ü.

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Original Article / Özgün Araştırma

Clinical and Ultrasonographic Evaluation of Masticatory Muscles in Young Subjects with and Without Bruxism

Bruksizmi Olan ve Olmayan Genç Bireylerde Çiğneme Kaslarının Klinik ve Ultrasonografik Olarak Değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate the stress levels and alterations in temporomandibular joint (TMJ) and masticatory muscle thickness determined by ultrasonography (USG) in young individuals with and without bruxism.

Materials and Methods: A total number of 63 eligible subjects were included. In both test (n=33) and control (n=30) groups, Fonseca Questionnaire, Beck's Depression inventory (BDI) were used as determinants of the presence of bruxism and stress levels. Clinical examination of TMJ and USG measurements of masticatory muscle thicknesses were recorded.

Results: Age, sex distribution, and BDI scores were comparable in the test and control groups ($p>0.05$). The presence of pain during palpation was significantly higher in TMJ (bilateral) and in masseter, temporal muscles, and temporal tendon (unilateral) of the test group ($p<0.05$). Masticatory muscle thicknesses, as determined by USG, were higher in the control group; however, the differences were not statistically significant ($p>0.05$).

Conclusion: As opposed to pain during palpation, USG evaluation revealed no differences in masticatory muscle thicknesses in young subjects with and without bruxism. Considering the rather young study sample, these results suggest that alterations in the stomatognathic system could occur in the long term.

Öz

Amaç: Çalışmanın amacı bruksizmi olan ve olmayan genç bireylerde stres seviyeleri ile temporomandibuler eklemde (TME) ve ultrasonografik olarak belirlenen çiğneme kas kalınlıklarında meydana gelen değişikliklerin değerlendirilmesidir.

Gereç ve Yöntemler: Çalışmaya, dahil edilme kriterlerine uyan toplam 63 birey dahil edilmiştir. Test (n=33) ve kontrol (n=30) gruplarında bruksizm varlığı ve stres seviyeleri sırasıyla Fonseca anketi, Beck Depresyon ölçeği (BDI) ile değerlendirilmiştir. TME'nin klinik muayenesi ve ultrasonografi (USG) ile çiğneme kaslarının kalınlık ölçümleri kaydedilmiştir.

Bulgular: Test ve kontrol grupları arasında yaş, cinsiyet dağılımı ve BDI skorları açısından istatistiksel olarak anlamlı fark gözlenmemiştir ($p>0,05$). Palpasyonda ağrı bulgusu TME'de çift taraflı olarak, masseter kas, temporal kas ve temporal tendonda ise tek taraflı olarak test grubunda kontrol grubuna göre anlamlı derecede yüksek

bulunmuştur (p<0,05). Çiğneme kas kalınlıklarının USG ile ölçümleri sonucunda ise kas kalınlıklarının kontrol grubunda test grubuna daha fazla olduğu, fakat bu farklılığın istatistiksel anlamlılık seviyesine ulaşmadığı gözlenmiştir (p>0,05).
Sonuç: Palpasyonda ağrı bulgusunun aksine, çiğneme kas kalınlıklarının USG ile ölçümü sonucunda her iki grup arasında istatistiksel olarak anlamlı fark gözlenmemiştir. Çalışma grubunu oluşturan bireylerin genç bireyler olmaları, bruksizme bağlı olarak gelişen kas hipertrofisinin uzun dönemde gerçekleştiğini düşündürmektedir.

Introduction

Bruxism is defined as "masticatory muscle activities that occur during sleep and wakefulness". Sleep bruxism is characterized as rhythmic or non-rhythmic, whereas awake bruxism is characterized by repetitive or sustained tooth contact and/or bracing or thrusting of the mandible (1). Bruxism is considered to be a parafunctional activity conducing pathological conditions in stomatognathic system such as pain, increased tonus in masticatory muscles and limited jaw movement, and it is considered to be a risk factor effecting temporomandibular joint (TMJ), as well. (2,3) Although, there are clinical studies reporting uni- or bilateral hypertrophy in masticatory muscles in subjects with long-term bruxism (3), there is conflicting data regarding the relationship between bruxism and masticatory muscle alterations (4). In a study evaluating the sleep bruxism related changes occurred in masseter and temporal muscles, it was reported that masticatory muscle functions were negatively affected, while there were no statistically significant differences in muscle thickness (5). In a recently published study, the thickness of mandibular adductor muscles in bruxism patients with and without tooth wear was evaluated by ultrasonography (USG), and it was concluded that masticatory muscle thickness was increased in the presence of bruxism (6). Among advanced imaging methods used for the examination of masticatory muscles, USG, is uncomplicated, low cost, applicable and reproducible method to analyze muscle function and thickness (7-9).

In 2013, a grading system is proposed for the diagnosis of bruxism. According to the grading system, possible sleep/awake bruxism is based on positive self-report, solely. Probable sleep/awake bruxism is based on positive clinical examination with or without the presence of positive self-report done, whereas, definite sleep/awake bruxism is based on a positive instrumental evaluation with or without the presence of a positive self-report and/or clinical inspection (1). Fonseca questionnaire, which was proposed to categorize the severity of temporomandibular disorders (TMDs), is a multi-dimensional assessment tool to obtain epidemiological data. It may also be employed for the self-reported assessment of bruxism along with clinical examination for diagnostic purposes (10).

Stress is suggested to play important role on bruxism, through the mechanism of neurotransmission from brain to masticatory muscles (11). Epidemiological studies reveal a prevalence rate increase from 5% to 22% among university students in 1966 and 2002, respectively (12). In a study evaluating the relationship between perceived stress and bruxism, it was reported that university students showed higher levels of bruxism and stress levels compared to the general population and positive correlation between stress and bruxism in male students (11).

Although, TMD is considered to be commonly seen clinical consequence of bruxism, there is not sufficient evidence to support this phenomenon. In a systematic review by Manfredini and Lobezzoo (2), it was suggested that clinical studies were required in order to clarify the association between bruxism and TMD. The authors emphasized the need for studies in which, diagnosis of bruxism is based on more quantitative and specific methods in order to avoid potential bias and confounding factors interfering with the outcomes.

The hypothesis of the current study is stress related bruxism affects TMJ and masticatory muscle thickness. The aim of our study is to evaluate the stress levels and alterations in both, TMJ and masticatory muscle thickness determined by USG in dental students with and without bruxism.

Materials and Methods

The study was conducted among dental students in Ankara University, Faculty of Dentistry between March 2019 and June 2019 according to the guidelines

of the Declaration of Helsinki (in full compliance with the ethical principles outlined in Helsinki Declaration). The study protocol was evaluated for ethical considerations and approved by the Non-Drug Clinical Trials Ethics Committee of Ankara University, Faculty of Dentistry (protocol no: 36290600/38, date: 26.09.2019). All participants were informed about the study protocol and informed consent was obtained before the initiation of the study.

Total number of 120 subjects were recruited for the study. Fonseca questionnaire was employed as a self-reported determinant of possible bruxism habit (13). Subjects with Fonseca score >45 was considered as bruxism patients (n=33) and included in the test group. Subjects for the control group (n=30) were randomly chosen among volunteer subjects who is not considered as bruxism patient according to Fonseca score. Volunteer subjects with full dentition and who signed the informed consent form were included in the study. Exclusion criteria were as follows: 1- Presence of periodontal disease, 2- presence of orthodontic anomalies which interfere with the occlusal relations, 3- being under orthodontic treatment or having it completed within the last 1 year, 4- history of maxillofacial surgery, 5- being under antidepressant medication.

Demographic data were collected, and depression levels defined by Beck Depression inventory (BDI) was evaluated in both test and control groups (14).

Fonseca questionnaire is composed of 10 questions which evaluate the presence of pain in TMJ, head, back and during chewing function, presence of parafunctional habits, limited movement, clicking, perception of malocclusion and sensation of emotional stress (10). BDI is a questionnaire consisting of 21 questions about depression symptoms. Every question is answered by choosing one of four responses that are scored between 0 and 3 points. According to BDI, scores ranging between 0 to 10 indicates minimal depression with no deviation from the norm. The scores between 11-16 are an indicator of mild depression. The scores from 17-20 is considered as an indicator of borderline of clinical depression and, the scores from 21 to 30 indicates moderate depression. Severe and extreme depressive disorder is indicated by the scores 31-40 and 41-63, respectively.

Clinical examination consisted of measurement of mandibular movement range, recording of TMJ sounds, and palpation of masticatory muscles and TMJ in both test and control groups. All clinical examinations and USG measurements were done by an experienced examiner (H.E). Mandibular movement range in over-jet, over-bite, left and right lateral and protrusive movements were measured in millimeters. Also, interincisal maximum mouth opening, forced mouth opening and pain free mouth opening measurements were performed. The presence TMJ sounds defined by clicking and palpation in left and right sides were recorded. The presence of pain during palpation of masseter, temporalis and lateral pterygoid muscles were recorded. The posterior mandibular, submandibular and temporal tendon sites were examined for the pain in palpation bilaterally.

Clinical evaluation was followed by USG analysis (Aloka Prosound Alpha-6, Hitachi, Tokyo, Japan) to evaluate the thickness of masticatory muscles. Bilateral linear evaluation of the thickness of masseter, temporalis and anterior portion of digastric muscles were performed by using 13-4 MHz linear probe, while 1-15 MHz hockey probe was used to evaluate the thickness of lateral pterygoid muscles. The subjects were seated with their heads resting on the headrest of the chair during the examination. The masseter muscle was imaged at the level of mandibular ramus and the widest distance in the posterior, middle and anterior margins were linearly measured. The anterior horizontal band of temporal muscle was transversally imaged between upper and outer border of orbita and anterior border of hairline and widest part is measured linearly. The lateral pterygoid muscle was imaged at transversal direction intraorally. After opening the mouth, the lateral pterygoid muscle which is attached to the lateral pterygoid plate, was observed as triangular shaped muscle and the distance between inner and outer parts at maxillary posterior buccal region is defined as its thickness. Anterior portion of digastric muscle was observed bilaterally by using the probe in transvers position on the outer surface of submandibular region and thickness of the muscle was measured. The measurements for masseter muscle were done at rest and clench positions (7,15,16).

Statistical Analysis

Statistical analyses were performed in SPSS (ver.24) statistics package program. Power for each

variable (strength of test) was set at least 0.80 and a type 1 error of 0.05 for sample width. Cohen's d in the calculation of effect size tested and d value was calculated as -0.89. As a result of the power analysis, minimum sample size was calculated as at least 25 subjects in each group. Thus, a sample size of at least 30 subjects for each group were included. Descriptive statistics for continuous variables were expressed as average, and standard deviation, values; categorical variables were expressed as number and percentage. Shapiro-Wilk's test was used to examine normality distributions of continuous variables. As a result, the data were found to have a normal distribution, so Independent t-test or Paired t-test (Paired) in paired comparisons was performed. Statistical significance level in calculations was taken as 5% (p=0.05).

Results

The age, gender distribution, Fonseca scores and BDI scores of the subjects are shown in Table 1. There were no statistically significant differences between test and control groups in terms of age (p>0.05). The female to male ratio was 5:28 and 10:20 in test and control groups, respectively. There were no significant differences between the study groups in the female to male ratio (p>0.05). Since, Fonseca scores were utilized as a determinant of bruxism, it was found to be statistically different between test and control groups (p<0.05). The test group revealed higher BDI scores, whereas the difference between the study groups did not reach the level of statistical significance (p>0.05).

Mandibular movement range measurements in over-jet, over-bite, left and right lateral movements, protrusion, interincisal maximum mouth opening, forced mouth opening and pain free mouth opening are shown in Table 2. There were no statistically significant differences between the test and control groups in any of parameters measured (p>0.05).

When bilateral TMJ sounds were evaluated, the presence of both clicking and crepitation sounds were found to be statistically significantly higher in the test group compared to the control group (p<0.05). There were no differences between left and right sides of TMJ in both groups (Table 3).

The presence of pain symptom during palpation was found to be significantly higher during the palpation of masseter muscle in the left side, temporal muscle in the right side and the temporal tendon in the right

Table 1. Comparison of the mean values of demographic data, Fonseca score and Beck's Depression inventory

	Test group (n=33)	Control group (n=30)
Age range (years)	21-24	20-25
Age (years) (mean ± standard deviation)	21.4±0.92	21.2±1.15
Gender (female/male)	5/28	10/20
Fonseca score (mean ± standard deviation)	59.39±12.73*	22.5±13.30
BDI (mean ± standard deviation)	12.8±7.25	10.80±7.40

*Statistically significant difference compared to control group (p<0.05), BDI: Beck Depression inventory

Table 2. Comparison of the mean value of mandibular movement range

	Test group (n=33)	Control group (n=30)
	Mean ± SD	Mean ± SD
Over-jet (mm)	2.64±1.40	2.42±1.08
Over-bite (mm)	2.98±1.61	3.57±1.71
Right lateral (mm)	8.33±2.86	7.87±2.78
Left lateral (mm)	8.06±2.42	8.07±3.18
Protrusion (mm)	7.09±4.63	6.53±2.70
Max mouth opening (mm)	46.33±5.89	46.7±35.52
Forced mouth opening (mm)	48.88±5.27	49.20±6.18
Pain free mouth opening (mm)	36.82±5.89	38.50±4.99

SD: standard deviation, no significant differences were found (p>0.05)

side (p<0.05). The presence of pain during the palpation of TMJ was found to be significantly higher bilaterally in the test group compared to control group (p<0.05). The test group presented higher percentages of positive pain symptom compared to control group in all examined sites, whereas statistical significance was observed only, in the aforementioned muscles and sides (Table 4). Pain in the masticatory muscles and TMJ due to alterations in the stomatognathic system is of importance for its negative impact on life quality (10).

The bilateral USG measurements has shown that the thickness of masseter muscle was both in rest and clenching positions was bilaterally higher in the control group compared to the test group (Figure 1), however the difference was not statistically significant (p>0.05). The thickness of temporal, lateral digastric and lateral pterygoid muscles were similar in both groups according to the bilateral USG measurements (p>0.05) (Table 5, Figure 2).

Table 3. Comparison of the percentage of the presence of TMJ sounds

	Test group (n=33)		Control group (n=30)	
	Left	Right	Left	Right
Clicking	72.72%*	69.69%*	43.33%	33.33%
Crepitation	27.27%	27.27%	3.33%	3.33%

*Statistically significant difference compared to control group (p<0.05)

Table 4. The percentage of the presence of pain during palpation

	Test group (n=33)		Control group (n=30)	
	Left	Right	Left	Right
Masseter	75.75%*	63.63%	33.33%	40.00%
Temporal	42.42%	42.42%*	20.00%	10.00%
TMJ	57.57%*	72.72%*	30.00%	26.66%
Posterior mandible	30.30%	36.36%	13.33%	20.00%
Submandibular	27.27%	27.27%	16.66%	10.00%
Lateral pterygoid	54.54%	63.63%	43.33%	43.33%
Temporal tendon	48.48%	63.63%*	30.00%	36.66%

*Statistically significant difference compared to control group (p<0.05), TMJ: Temporomondibular joint

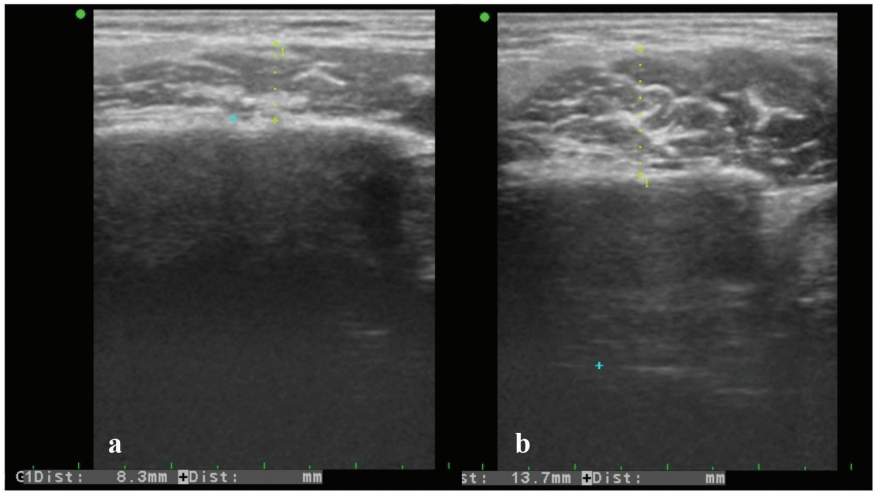

Figure 1. Ultrasonographic appearance of masseter muscle in rest **(a)** and clenching **(b)** positions. Approximately 5,4 mm increase in thickness of masseter muscle is clearly seen in clenching position

Table 5. The mean value of ultrasonography measurements of masticatory muscle thicknesses				
	Test group (n=33)		Control group (n=30)	
	Mean SD		Mean SD	
	Left	Right	Left	Right
Masseter (at rest)	7.10±1.20	7.6±1.25	7.97±1.79	7.91±1.77
Masseter (clenching)	11.67±2.03	11.81±1.93	12.89±2.59	12.79±2.55
Temporal	10.23±1.88	10.54±1.98	10.33±1.68	10.98±1.90
Lateral digastric	5.52±0.95	5.85±0.99	5.95±1.46	6.61±1.48
Lateral pterygoid	5.41±0.80	5.60±0.55	5.52±0.83	5.45±0.64
SD: Standard deviation, no significant differences were found (p>0.05)				

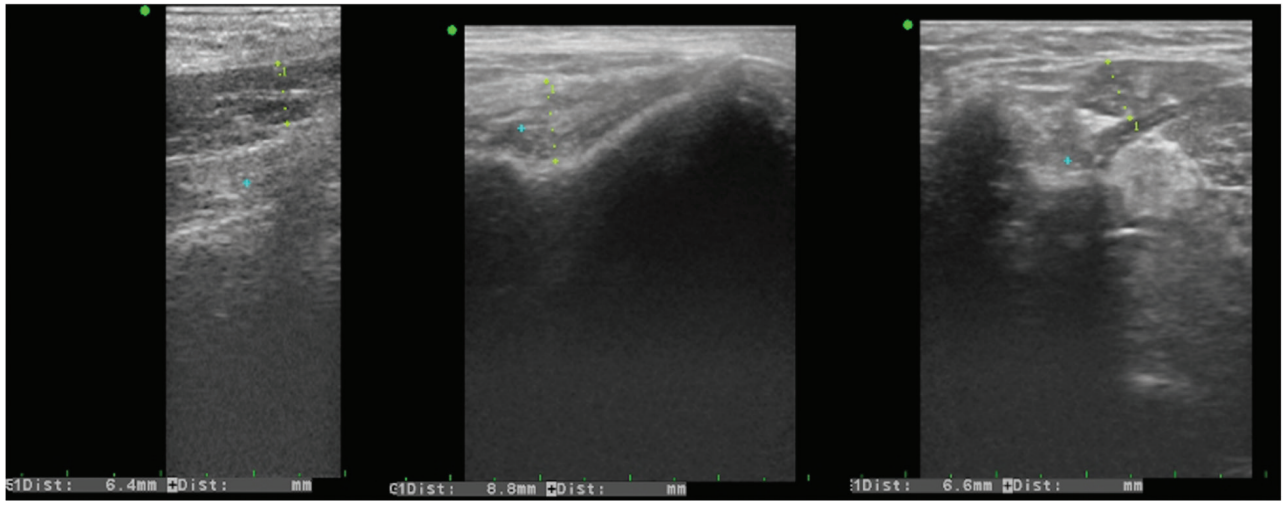

Figure 2. Ultrasonographic images of lateral pterygoid **(a)**, temporal **(b)** and anterior portion of digastric **(c)** muscles with thickness measurements

Discussion

In this cross-sectional study, we hypothesized that stress related bruxism affects TMJ and masticatory muscle thickness and the aim of our study is to evaluate the stress levels and clinical alterations in TMJ and masticatory muscles and also the effect of bruxism on masticatory muscle thickness determined by USG in dental students with or without bruxism. The Fonseca's questionnaire was used as a self-reported determinant of bruxism (10). The questionnaire is composed of 10 questions that are answered with "yes", "no" or "sometimes" and each question should be answered by only one answer. The lack of time limitation to complete the questionnaire prevents induced answers by the subjects. Fonseca scores between 0-15 is related to no TMD, the scores from 20 to 40 is related to mild TMD, from 45 to 65 is related to moderate TMD and the scores from 70 to 100 is considered as sign of severe TMD. In our study, among 120 dental students who have completed the Fonseca's questionnaire, total number of 33 subjects with the Fonseca score >45 are considered as bruxism patients. In a study by Nomura et al. (17), Fonseca's questionnaire was used to evaluate 218 dental students and 35.78% of the subjects were found to have mild levels of TMD, 11.93% of the subjects were found to have moderate levels of TMD and only 5.5% of the participants had severe TMD. In another study conducted among dental students (n=409), the severity of TMD was mild in 38.6% of the subjects, moderate in 13.4% of the subjects and severe in 4.4% of the subjects (13). In the current study, 20% of the all subjects included had moderate levels of TMD and 7.5% of the subjects had severe levels of TMD. The

percentages of subjects with moderate and severe TMD is found to be comparable with the similar studies which were conducted in dental students. Since, the test group was constituted of subjects with scores higher than 45, the difference of the Fonseca score between the test and control groups were statistically significant, as expected. The employment of questionnaires designed to assess bruxism are considered among non-instrumental approaches and self-reported assessment of bruxism is still the primary tool in the assessment of bruxism for both clinical and research purposes. The possible limitation of self-report is the complex relationship of bruxism and psychological factors (1). In the current study, the difference between the stress levels of test and control groups were not statistically significant, therefore we may assume that the subjects' stress levels did not interfere with their perception of bruxism.

The BDI scores were 12.8±7.25 and 10.80±7.40 in test and control groups, respectively. Although, the stress levels defined by BDI is higher in the test group compared to the control group, the difference was not statistically significant. The relationship between stress and bruxism has been studied extensively, and there are many studies indicating a positive correlation in between (18). In a study evaluating the behavior profile of children with bruxism, it was suggested that potential emotional problems could be risk factors of bruxism in children (19). In another study by Serra-Negra et al. (20), the relationship between stress levels, personality traits, and sleep bruxism in children were evaluated and it was reported that stress high levels were effective on sleep bruxism development in children. There are also some studies reporting partial relationship between stress and bruxism. Cavallo et al. (11), evaluated the prevalence of awake and sleep bruxism and concluded that there was a positive correlation between perceived stress and bruxism only in male gender and they also reported that university students had higher stress levels compared to general population. In a study examining the job associated psychological stress and sleep bruxism reported weak relationship between stress and bruxism in men (21). Ohlmann et al. (22), conducted a study in order to assess the association between sleep quality, the presence of chronic stress and sleep bruxism and have shown no significant relationship. Likewise, our results did not reveal any differences in the stress levels of subjects with or without bruxism.

Bruxism causes some alterations in the stomatognathic system structure. As a result, there may be pain in the palpation of TMJ and the presence of sounds from the joint. The lack of lateral pterygoid muscle coordination, the change in capitulum mandibula, vertical dimension loss and mandibular displacement may be the reason for the clinical symptoms (23). In our study, the percentage of the presence of TMJ sounds as clicking and crepitation were significantly higher in the test group compared to the control group, whereas there were no differences between the left and right sides in both groups. In a study evaluating the self-reported bruxism and associated factors, the prevalence of subjects reporting the presence of oro-facial pain, neck pain and joint sounds were similar (24). Although, the results of aforementioned study are based on self-reported data rather than clinical examination, the similarity in the prevalence of TMJ sound and TMD supports association between bruxism and joint sound.

Pain in the masticatory muscles and TMJ due to alterations in the stomatognathic system is of importance for its negative impact on life quality (10). There are studies supporting the association of bruxism and pain symptom. In a study by Huang et al. (25), an association between myofascial pain and self-reported bruxism with an odds ratio of 4:8 was reported. In another study evaluating the perceived orofacial pain associated to reported bruxism, positive association was demonstrated (26). Similarly, in our study subjects with bruxism revealed to have higher percentages of positive pain in palpation results compared to the control group, however statistically significance was observed in the left masseter muscle, in the right temporal muscle, in the right temporal tendon and in the both sides of TMJ. However, it should be kept on mind that the mechanisms of pain and bruxism association is complex and data in the current literature should be interpreted carefully, since most of data presented are obtained from studies using self-reported measures of bruxism.

In the current study, USG was used to determine the masticatory muscle thicknesses. USG is an accurate, uncomplicated and affordable diagnostic method used to evaluate the thickness of the head

and neck muscles (27). Results of our study did not reveal statistically significant difference in the thicknesses of any masticatory muscle measured in young patients with and without bruxism. However, thickness of masseter muscle was higher in the control group in both sides at rest and clenching while the thicknesses of temporalis, lateral digastric and lateral pterygoid muscles were similar in both of the study groups. It has been suggested that in subjects with bruxism increased forces on masticatory muscles may result with hypertrophy (28). In their study, Mäntyvaara et al. (29) compared the occlusal forces in bruxism patients and healthy controls and reported higher occlusal forces in the test group. Goller Bulut et al. (6), performed the USG evaluation of jaw elevator muscles in bruxism patients with and without tooth wear and they concluded that the occlusal forces, tooth wear and the thickness of masticatory muscles were increased in bruxism patients. On the contrary, Adisen et al. (4) compared the masticatory muscle volumes determined by magnetic resonance images and occlusal force distributions in patients with bruxism and healthy controls. The authors concluded that masticatory muscle hypertrophy was not a sign of sleep bruxism in young patients. As in our study, Palinkas et al. (5), employed USG in order to compare the muscle thickness in patients with and without sleep bruxism. The authors reported that there were no statistically significant differences between the study groups which is similar to our study. We assume that rather young population included in our study is accountable for the lack of significant difference between the study groups, as it may take longer period for the dimensional alterations in the masticatory muscles to occur. In our study, occlusal forces were not evaluated, therefore it is not possible to make an interpretation about its possible role on the insignificant differences in the muscle thickness.

Conclusion

In dental students with and without bruxism, there were no differences between the stress levels and masticatory muscle thicknesses between the test and control groups. However, differences in pain symptom during palpation of TMJ, masseter and temporal muscle may suggest that alterations in stomatognathic system occur in long term. There is need for further studies in larger sample size and different age groups.

Ethics

Ethics Committee Approval: The study was conducted among dental students in Ankara University, Faculty of Dentistry between March 2019 and June 2019 according to the guidelines of the Declaration of Helsinki (in full compliance with the ethical principles outlined in Helsinki Declaration). The study protocol was evaluated for ethical considerations and approved by the Non-Drug Clinical Trials Ethics Committee of Ankara University, Faculty of Dentistry (protocol no: 36290600/38, date: 26.09.2019).

Informed Consent: All participants were informed about the study protocol and informed consent was obtained before the initiation of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: H.E., N.B., B.B., Design: H.E., Supervision: H.E., Data Collection or Processing: H.E., N.B., Analysis or Interpretation: H.E., N.B., B.B., Literature Search: H.E., N.B., B.B., Critical Review: H.E., N.B., B.B., Writing: B.B.

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

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Original Article / Özgün Araştırma

Can Preoperative Haematological Parameters Predict Pathology Results in Patients Undergoing Open Prostatectomy Due to Benign Prostatic Hyperplasia? A Retrospective Study

Benign Prostat Hiperplazisi Nedeniyle Açık Prostatektomi Uygulanan Hastalarda Preoperatif Hematolojik Parametreler Patoloji Sonuçlarını Öngörebilir mi? Retrospektif Bir Çalışma

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Keywords
Prostate cancer, open prostatectomy, benign prostatic hyperplasia, lymphocytes, neutrophils

Anahtar Kelimeler
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Abstract

Objective: Although the incidence of incidental prostate cancer (IPCa) has decreased in patients undergoing open prostatectomy with the increasing use of prostate-specific antigen (PSA), cases of IPCa are still reported. This study aimed to investigate the rate of IPCa in our patients who underwent open prostatectomy and to find the relationship between haematological parameters and pathology results.

Materials and Methods: Data of patients who underwent open prostatectomy in our urology clinic between January 2014 and December 2019 were retrospectively investigated. Patient age, preoperative PSA level, prostate volume, post-void residual urine volume, history of urethral catheterisation, presence of accompanying bladder stones, pathology results of prostate biopsy, post-operative pathology results, haematological parameters, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were evaluated.

Results: A total of 83 male patients were included in the study. The mean patient age was 68.89±6.72 years. The mean preoperative PSA value was 7.46±6.23 ng/mL. Benign prostatic hyperplasia was detected in the post-operative pathology results of all patients; however, prostate adenocarcinoma was found in six (7.2%) and chronic prostatitis accompanied with benign prostatic hyperplasia was detected in 46 (55.4%) patients. PLR and NLR were higher in patients with IPCa than in patients without IPCa. The difference was statistically significant in terms of PLR (p=0.010). By contrast, the mean lymphocyte count was significantly lower in patients with IPCa than in those without IPCa (p=0.009).

Conclusion: This study showed that the rate of IPCa in our clinic was similar to that in literature. Results suggest that evaluation of preoperative haematological parameters in patients who underwent open prostatectomy may guide urologists and pathologists in predicting pathological conditions.

Öz

Amaç: Prostat spesifik antijen (PSA) kullanım sıklığının artması ile açık prostatektomi uygulanan hastalarda insidental prostat kanseri (İPK) görülme sıklığı azalmış olsa da devam etmektedir. Bu çalışmanın amacı, açık prostatektomi uygulanan hastalarımızda İPK oranı ve hematolojik parametreler ile patoloji sonuçları arasında bir ilişki olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Ocak 2014 - Aralık 2019 tarihleri arasında üroloji kliniğimizde açık prostatektomi geçiren hastaların verileri geriye dönük olarak incelendi. Hastaların yaşı, ameliyat öncesi PSA değeri, prostat hacmi, işeme sonrası rezidüel idrar miktarı, üretral kateterizasyon öyküsü, eşlik eden mesane taşı varlığı, prostat biyopsisinin patoloji sonuçları, post-operatif patoloji sonuçları, hematolojik parametreler ve nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (PLO) değerlendirildi.

Bulgular: Çalışmaya toplam 83 erkek hasta dahil edildi. Hastaların ortalama yaşı 68,89±6,72 yıldı. Preoperatif ortalama PSA değeri 7,46±6,23 ng/mL idi. Tüm hastaların post-operatif patoloji sonuçlarında benign prostat hiperplazisi saptanırken, 6 hastada (%7,2) prostat adenokarsinomu ve 46 hastada (%55,4) kronik prostatitin benign prostat hiperplazisine eşlik ettiği görüldü. İPK'li hastalarda, İPK olmayan hastalara göre PLO ve NLO'nun daha yüksek olduğu görüldü. Bu yükseklik PLO açısından istatistiksel olarak anlamlıydı (p=0.010). Öte yandan, ortalama lenfosit sayısı İPK olan hastalarda İPK olmayan hastalara göre anlamlı olarak daha düşüktü (p=0,009).

Sonuç: Bu çalışma, kliniğimizde İPK oranının literatürdekine benzer olduğunu göstermiştir. Ayrıca sonuçlar, açık prostatektomi uygulanan hastalarda preoperatif hematolojik parametrelerin değerlendirilmesinin ürologlar ve patologlar için patoloji sonuçlarını tahmin etmede yol gösterici olabileceğini düşündürmektedir.

Introduction

Benign enlargement of the prostate as a result of the proliferation of smooth muscle and epithelial cells in the area of the prostate closest to the urethra, called as the transitional zone, is benign prostatic hyperplasia (BPH). The enlargement of the prostate and cell proliferation cause lower urinary tract symptoms (LUTS) by narrowing the urethral lumen. BPH is the most common benign neoplasm in aging men. While it occurs about 8% of men in their 40s, this rate rises to 90% for men over 90 years old (1).

In addition to medical treatment options, there are surgical treatment options in the treatment of patients with LUTS due to BPH (2). Advances in the surgical techniques over the years have given rise to the widespread use of minimally invasive techniques in surgical treatment of BPH (2). However, open prostatectomy is still an alternative surgical treatment to minimally invasive treatments with a strong degree of recommendation in the guidelines for men with absolute or relative surgical indications and prostate volume >80 mL (2,3). Open prostatectomy is still the gold standard surgical treatment in large prostates in many clinics where endoscopic enucleation techniques cannot be applied.

The rate of incidental prostate cancer (IPCa) decreased with increasing frequency of the use of prostate-specific antigen (PSA). However, it has been reported in various studies that the rates of IPCa varied between 1.4-16.7%, according to the pathology samples of the patients undergoing prostate surgery (4,5).

In addition to their use as indicators of systemic inflammatory response in many studies (6,7), it was investigated whether neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were effective in predicting oncological outcomes in malignancies (8).

In this study, it was aimed to identify the rate of IPCa in our clinic and to determine whether NLR and PLR, which are hematological parameters, are predictive factors in predicting pathology results by examining the pathology results of patients who underwent open prostatectomy in our clinic.

Materials and Methods

Following the approval of the Aydın Adnan Menderes University Non-Interventional Clinical Research Ethics Committee (decision no: 11, date: 06.08.2020), the data of patients who underwent open prostatectomy due to BPH between January 2014 and December 2019 in our hospital were retrospectively analyzed. The study protocol was designed in compliance with the Declaration of Helsinki. Informed consent was obtained from patients.

All patients who underwent open prostatectomy in our clinic were included in our study, regardless of whether they had preoperatively undergone transrectal ultrasound-guided biopsy (TRUS-Bx) (whose pathology was not prostate adenocarcinoma) or not.

Patients' age, preoperative PSA value, estimated prostate volume (EPV), post-void residual urine (PVR), history of urethral catheterization, presence

of accompanying bladder stones, prostate biopsy pathology results if performed, and post-operative pathology results were evaluated. In addition, leukocyte, lymphocyte, neutrophil and platelet counts obtained from preoperative routine hematological laboratory results, and the NLR and PLR calculated from these data were assessed.

Serum PSA was collected from final laboratory results just before biopsy procedures were performed in those undergoing prostate biopsies. Serum PSA was collected from the last laboratory results just before open prostatectomy was performed in patients without prostate biopsy. We collected EPVs, PVRs and presence of accompanying bladder stones from their initial trans-abdominal ultrasound reports. The NLR and PLR were obtained by dividing the absolute neutrophil count or platelet count directly towards their absolute lymphocyte count. Patients whose data could not be reached or were incomplete were excluded from the study.

Statistical Analysis

IBM SPSS Statistics for Windows version 25 (IBM Corp., Armonk, NY) was used for data analysis. Kolmogorov-Smirnov test was used as the test of normal distribution. In the statistical analysis, student's t-test was used for normally distributed data and Mann-Whitney U test for data not distributed normally. Chi-square test was used in the comparison of categorical data, and the level of significance was taken as 0.05 for all tests.

Results

A total of 83 male patients with an age ranging from 55 to 84 years were included. The mean age of the patients was 68.89±6.72 years. The mean PSA level and the mean EPV were 7.46±6.23 ng/mL and 107.3±38.7 mL, respectively. The mean PVR was 208.67±172.43 mL and ranged between 30 to 840 mL. (Table 1). It was observed that preoperative urethral catheterization was performed in 72.3% of patients (n=60) and bladder stones were detected in 17 patients (20.5%). Preoperative TRUS-Bx was performed in 27 patients (32.5%). In the patients with TRUS-Bx, the mean PSA level was 14.02±6.50 ng/mL and the mean EPV was 114.59±39.68 mL. The mean PSA level of the patients with TRUS-Bx was significantly higher compared to the patients without TRUS-Bx (4.30±2.57) ($p<0.05$). The mean age of the patients with TRUS-Bx was significantly lower compared to the patients without TRUS-Bx (66.37±5.46 years vs 70.11±6.97 years, respectively) ($p<0.05$). Based on the evaluation of patients' pathology results, in addition to the diagnosis of BPH in all patients, prostate cancer was detected in 6 patients (7.2%) and chronic prostatitis in 46 patients (55.4%). In three patients with IPCa, TRUS-Bx was not performed before the surgey since PSA levels were normal and there was no suspicious finding in the rectal examination. However, it was performed in the remaining three patients. It was seen that the mean PSA level and the mean EPV in the patients with IPCa were 9.85±6.39 ng/mL and 119.67±23.75 mL, respectively. The lymphocyte counts of the patients without IPCa (2.73±0.71) were higher than those with IPCa (1.89±0.64), and this difference was statistically significant ($p=0.009$). The mean PLR in the patients with IPCa (158.13±79.02) was significantly higher than that in the patients without IPCa (80.82±18.01) ($p=0.010$) (Table 1). IPCa was in Gleason score 3+3=6 in all patients and no increase in PSA was detected in any of them, although they received no additional treatment. There was no significant difference in terms of PSA levels, EPV, PVR, leukocyte, neutrophil, platelet and lymphocyte counts, as well as NLR, PLR among patients with and without chronic prostatitis (Table 2).

Discussion

Open prostatectomy is a treatment procedure which has a strong recommendation by guidelines

Table 1. Patient baseline characteristics

Characteristic	n=83
Age (years)	68.89±6.72 (55-84)
PSA (ng/dL)	7.46±6.23
EPV (mL)	107.3±38.7 (46-225)
PVR (mL)	208.67±172.43 (30-840)
Leucocyte count ($x10^3/mm^3$)	8.41±2.49
Neutrophil count ($x10^3/mm^3$)	5.61±2.19
Lymphocyte count ($x10^3/mm^3$)	1.94±0.67
Platelet count ($x10^3/mm^3$)	261.92±71.42
NLR	3.43±3.16
PLR	152.54±78.82

PSA: Prostate-spesific antigen, EPV: Estimated prostate volume, PVR: Post-void residual urine, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

Table 2. The comparisons of groups with regard to clinical characteristics and hematological parameters of the patients

	Chronic prostatitis			Incidental prostate cancer		
	Patients with CP (n=46)	Patients without CP (n=37)	p	Patients with IPCa (n=6)	Patients without IPCa (n=77)	p
Age (years)	68.72±7.47	69.11±5.74	0.794	67.50±4.037	69.00±6.89	0.601
PSA (ng/dL)	7.89±5.59	6.94±6.99	0.134	9.85±6.39	7.28±6.22	0.235
EPV (mL)	102.34±37.52	113.51±39.75	0.124	119.67±23.75	106.36±39.56	0.421
PVR (mL)	233.08±207.23	178.32±111.06	0.433	181.17±117.25	210.82±176.38	0.937
Leucocyte count ($x10^3/mm^3$)	8.57±2.70	8.21±2.22	0.611	8.33±2.52	9.45±1.99	0.120
Neutrophil count ($x10^3/mm^3$)	5.87±2.54	5.29±1.66	0.336	5.59±2.25	5.87±1.35	0.351
Lymphocyte count ($x10^3/mm^3$)	1.85±0.68	2.07±0.66	0.127	1.89±0.64	2.73±0.71	0.009*
Platelet count ($x10^3/mm^3$)	268.85±73.09	253.30±69.32	0.327	265.43±71.26	216.83±62.11	0.109
NLR	4.05±4.72	2.68±0.83	0.079	3.53±3.73	2.23±0.62	0.086
PLR	167.56±91.41	133.87±55.31	0.056	158.13±79.02	80.82±18.01	0.010*

CP: Chronic prostatitis, IPCa: Incidental prostate cancer, PSA: Prostate-spesific antigen, EPV: Estimated prostate volume, PVR: Post-void residual urine, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio

*p<0.05 Intergroup significant difference, Mann-Whitney U test

for patients with bladder outlet obstruction with a prostate volume >80 mL (2,3). However, as a result of advances in laser technology and minimally invasive surgical technique, holmium laser enucleation of the prostate (HoLEP) has taken its place in surgical treatment with similar success rates and a strong recommendation in the guidelines (2). While IPCa was detected in quite high rates in the past, the rate of prostate biopsy has been increased due to the widespread use of PSA and of different combinations of its forms. Therefore, the IPCa detection rate has decreased significantly recently (4,5). Although the rate of IPCa is decreasing today, it is important to determine the predictive factors in terms of diagnosis and treatment planning. We evaluated some clinical and laboratory parameters in addition to PSA in order to detect IPCa in cases undergoing open prostatectomy and this study demonstrated that the lymphocyte counts and PLR were predictive factors in predicting pathology results.

In the study of Otsubo et al. (9) consisting of 365 patients undergoing HoLEP and in the study of Güner and Şeker (10) in 124 patients undergoing open prostatectomy, the rates of IPCa were 6.8% and 4%, respectively. In addition, while there were significant differences in terms of the EPV and preoperative PSA levels between the patients with BPH and IPCa in the study of Otsubo et al. (9), no significant difference was observed in terms of these two parameters in the study of Güner and Şeker (10). In agreement with the study of Güner and Şeker (10), this study detected that there was no significant difference between the patients with BPH and IPCa in terms of the EPV and preoperative PSA levels. In addition, the present study showed that the rate of IPCa was 7.2% similar to the rates in those two previous studies.

It is known that the PSA level is not sufficient alone in detecting prostate cancer because it also increases in common diseases such as BPH and prostatitis (11). NLR and PLR, potential markers for determining inflammation, are used for differential diagnosis or prognostic predictors of various diseases such as cancer and inflammatory diseases in many studies (12,13). Leukocytes, mainly lymphocytes, are one of the most significant markers in many cancers, apart from prostate cancer (12,13). Several studies reported that lymphocyte levels were lower in prostate cancer (13-15). In this study, we also showed that the lymphocyte counts were significantly lower in the patients with IPCa (p=0.009). Although there was no significant difference (p=0.086), the mean NLR was higher in the patients without IPCa, similar to the other studies (13,15,16). As it was demonstrated in previous studies, a significant difference was observed

in terms of PLR between the patients with or without IPCa (13,15,17,18) and it was found to be higher in the patients with IPCa (p=0.010). These results suggest that preoperative PLR, NLR, and lymphocyte counts may be an important predictor of IPCa in patients scheduled for open prostatectomy.

Similar to the previous studies which demonstrated an increase in these parameters in case of inflammation in the patients with chronic prostatitis (12,19), when the patients were divided into two groups according to the presence of chronic prostatitis, although there was no significant difference in terms of leukocyte, neutrophil, platelet counts, NLR and PLR between the patients with and without chronic prostatitis, these parameters were higher in the patients with chronic prostatitis. It has been shown that lymphocyte levels decrease and neutrophil counts increase in systemic inflammatory response (19). In this study, it was observed that lymphocyte counts were insignificantly lower in the patients with chronic prostatitis.

This study had some limitations such as being a retrospective study and being conducted in a single center with a small number of patients. On the other hand, we showed that the rate of IPCa in our urology clinic was similar to the literature. In addition, despite these limitations, one of the strengths of our study is that there was a significant relationship between hematological parameters and pathology results in patients who underwent open prostatectomy. Multicenter prospective studies with a larger number of patients to be conducted in the future will eliminate the limitations of this study and more clearly reveal the relationship between hematological parameters and pathology results.

Conclusion

Although the incidence of the IPCa has decreased in the patients undergoing open prostatectomy due to bladder outlet obstruction and/or LUTS with the increase in the frequency of use of PSA, it continues. Therefore, the rate of IPCa in our study was found to be similar to the literature. Evaluation of preoperative PSA level, as well as hematological parameters such as neutrophil, lymphocyte and platelet counts, NLR, and PLR in the patients who will undergo open prostatectomy will provide both urologists to review their preoperative approaches, and pathologists to examine pathology specimens more carefully in terms of prostate cancer.

Ethics

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Non-Interventional Clinical Research Ethics Committee (decision no: 11, date: 06.08.2020).

Informed Consent: Informed consent was obtained from patients.

Peer-review: Externally peer-reviewed.

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Original Article / Özgün Araştırma

Protective Effect of Vitamin B5 (Dexpanthenol) on Nephropathy in Streptozotocin Diabetic Rats

Sıçanlarda B5 Vitamininin (Dekspantenol) Nefropatiye Etkisi

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Keywords
Cytokines, panthenol, pantothenic acid, pantothenol, streptozotocin

Anahtar Kelimeler
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Abstract

Objective: This study aimed to evaluate the effects of vitamin B5 [dexpanthenol, DEX] treatment on the kidney in a streptozotocin (STZ) diabetes animal model.
Materials and Methods: Twenty-four Wistar rats were randomised in one of the four groups: Group 1 served as control, and group 2 was administered high-dose DEX (300 mg/kg/day) as a safety group. Diabetes was induced by intraperitoneal injection of a single dose of STZ (50 mg/kg) in groups 3 and 4. In group 4, DEX was administered as well. All groups were followed up for 6 weeks. Histopathological analyses were performed on renal tissue using periodic acid-Schiff and Hematoxylin-Eosin stains.
Results: Microscopic evaluation of the kidney revealed that the rats demonstrated kidney damage 6 weeks after STZ administration. However, high-dose and long-term DEX administration alone did not damage renal tissue; moreover, kidney damage was prevented if DEX was administered in the early phase of diabetes.
Conclusion: DEX could be a safe and cost-effective vitamin for the prevention of diabetes complications.

Öz

Amaç: Çalışmamızda streptozotosin (STZ) diyabet hayvan modelinde B5 [dexpanthenol (DEX)] vitamini ile tedavinin böbrek üzerindeki etkilerini değerlendirdik.
Gereç ve Yöntemler: Yirmi dört wistar sıçanı dört gruba eşit ve randomize olarak dağıtıldı. Grup 1 kontrol grubu; grup 2 güvenlik grubu olarak yüksek doz DEX (300 mg/kg/gün) verildi. Diyabet, grup 3 ve 4'te tek bir intraperitoneal doz STZ (50 mg/kg) enjeksiyonu ile oluşturuldu. Grup 4 DEX ile tedavi edildi. Tüm gruplar 6 hafta takip edildi. Periyodik asit Schiff ve Hematoksilen-Eosin kullanılarak böbrek dokusu üzerinde histopatolojik incelemeler yapıldı.
Bulgular: Böbreğin mikroskobik değerlendirmesinde, sıçanlarda STZ müdahalesinden 6 hafta sonra böbrek hasarı geliştiği görüldü. Tek başına yüksek ve uzun süreli DEX uygulaması böbrek dokusu için zararlı değildi. Ayrıca diyabetin erken evresinde DEX verilmesi böbrek hasarını önledi.
Sonuç: Diyabet komplikasyonlarını önlemek için DEX güvenli ve uygun maliyetli bir vitamin olabilir.

Introduction

Diabetic nephropathy (DN) is seen in approximately 40% of diabetic patients as being one of the major long-term microvascular complications (1). And characterized with high blood pressure, albuminuria and progressive renal damage that leads to end stage renal failure (2). Metabolic and hemodynamic factors were thought to be the main mechanisms of the diabetes and DN; however, it has been shown that chronic inflammation caused by immunologic and inflammatory mechanisms may have a significant role in the development and progression of the disease (3). Worldwide the number of diabetes patients and patients with DN, are highly increasing and more and more patients will unfortunately be experiencing end-stage renal disease, therefore, it is highly important to investigate and prevent progressive renal disease with the effective treatments (1).

Streptozotocin (STZ) is the main chemical agent used for the induction of diabetic metabolic state in experimental animals (4,5).

Most of the protective effects of pantothenic acid and its reduced derivative, dexpanthenol (DEX) (pantothenol, panthenol) are attributed to its modulator activity on antioxidant capacity (6-8). Decreased apoptosis rate (9), increased coenzyme A (10) and adenosine triphosphate (ATP) synthesis (11) have been reported as well. Bayrak et al. (12) have reported DEX might be a new therapeutic approach by reducing the inflammation and cell infiltration in interstitial cystitis. Meanwhile, increased rate of urinary excretion of pantothenic acid has been reported in both animal model and patients with diabetes in 1967 (4). Since then, the studies conducted regard to the matter of vitamin B5's effect on DN are scarcely close to none. In the present study, we investigated the effect of DEX supplementation on the reversal of STZ-induced DN in rats.

Materials and Methods

Experimental Procedure

Twenty-four male Wistar rats, each weighed 220-240 g, were provided by Aydın Adnan Menderes University, Experimental Animal Center and all experiments were designed and done being in line with the principles and guidelines of Aydın Adnan Menderes University Animal Ethics Committee's approval (decision no: HEK/2009/64, date: 02.09.2009). The animals were randomly divided in to four groups: The rats in the control group served as healthy animals and the DEX group has taken only intraperitoneal 300 mg/kg DEX once a day for six weeks. The other two groups have injected a single intraperitoneal dose of STZ (50 mg/kg in 1 mL of saline). STZ applied rats with over than 200 mg/dL blood sugar levels (IME-DC® Glucosticks) 72 h after the injection were considered diabetic. STZ+DEX group was treated daily DEX (300 mg/kg) for six weeks as well. DEX doses of animals were adjusted every monday according to their weight changing during 6 weeks. Under the anaesthesia of ketamine and xylasine (50 mg/kg and 5 mg/kg, respectively), kidney tissues were obtained and fixed in 10% neutral buffered formalin solution.

Histological Assessment of Renal Tissue

Kidney tissues embeded into paraffin and afterwards stained with hematoxylin and eosin and periodic acid Schiff (PAS). A bright-field microscope was used to examine these preparations and then photographs were taken (Carl Zeiss Axio Lab A1, Germany). Statistical analysis was not used in the study.

Results

We explained our results by dividing them into two groups histopathologically and histochemically

Histopathological Findings

In groups control and DEX-treated rats (Figure 1A-B), normal renal tubular architecture and normal glomeruli were observed. In the STZ-treated rats (Figure 1C), it was observed that Bowman spaces of a number of glomeruli were narrowed, mesangial matrix was enlarged and tubular dilatations were seen. Additionally; falling of the epithelial cells to the lumens of tubules and Armanni-Ebstein lesions were determined. When compared, the renal structural alterations in STZ+DEX-treated (Figure 1D) rats, were less obvious than the untreated diabetic rats.

Histochemical Findings

When compared with control and DEX animals, in the renal histology in untreated diabetic rats, accelerated mesangial expansion, tubular dilatation,

thickening of capsular basement membranes (CBMs), glomerular basement membranes (GBMs), and tubular basement membranes (TBMs) which are characterized by an increase in PAS-positive area, were observed (Figure 2A-B). When compared with untreated diabetic group, it is seen that the treatment of DEX, reduced the glomerular size; thickening of CBMs, GBMs, and TBMs; increased amounts of mesangial matrix; and tubular dilatation (Figure 2C-2D).

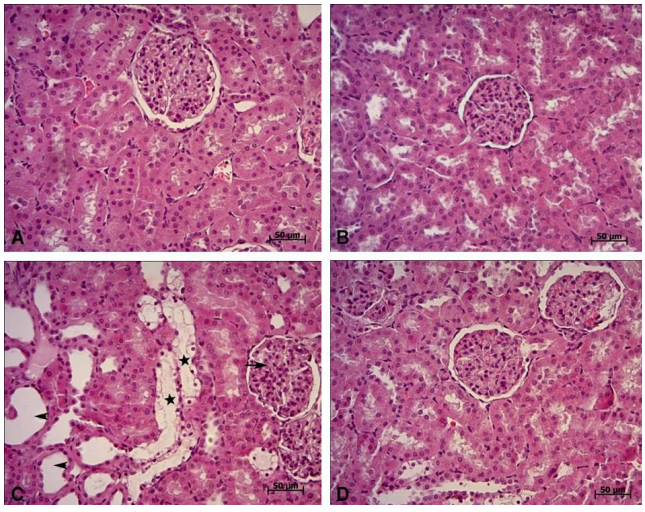

Figure 1. Representative micrographs of rat kidney sections stained with Hematoxylin-eosin. **(A-B)** Normal kidney morphology of control and DEX treated rats. **(C)** streptozotocin-treated rats, showing mesangial matrix enlargement (arrow), tubular dilatations (arrowheads) and Armanni-Ebstein lesions (asterisks). **(D)** DEX-treated diabetic rats, close to normal architecture and low tubular damage. Scale bar, 50 µm

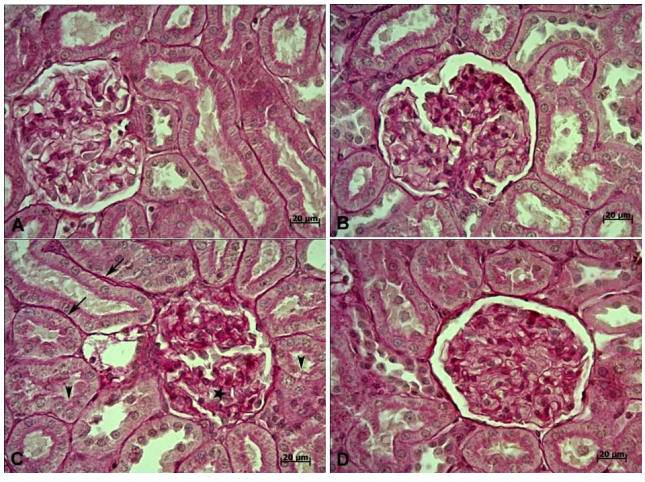

Figure 2. Pediatric acid Schiff **(**PAS) staining of kidney sections of control (**A)**, dexpanthenol (DEX) **(B)**, streptozotocin (STZ) (C), STZ+DEX **(D)** rats. In the STZ-treated group **(C)**, increase in mesangial matrix (asterisk), thickening basal membranes (arrows), shorting and ruptures at the brush border (arrowheads) were seen. Scale bar, 20 µm.

Discussion

In the present study, we considered the possibility that supplementation of DEX, a source of pantothenic acid, might prevent the kidney injury observed in STZ rats. Concerning this hypothesis, we have preferred to use pantothenic acid's high amount of dose to see its safety on the kidney. Histopathologic examination revealed that even if it is taken in long term and high dose, it does not show any adverse effect on the renal tissue. It has been investigated cardiovascular and liver effect of DEX, clinical and biochemical findings have been previously given (13,14). Here, we particularly focused on histopathological evaluation on kidney for avoiding repeating of the data.

STZ is well accepted model of animal diabetes and the toxin can damage the kidney due to inhibition of glucose transporter expression (5). This study has been shown that 6-week was sufficient period to develop a remarkable injury following to the induction of STZ. Introducing treatment of DEX in the early phase of STZ diabetes was highly prevented the progression of DN. These results are in agreement with the previous literatures. One of earlier study about the relationship between diabetic kidney and pantothenic asid demonstrated the increased urinary loss of pantothenic acid and claimed that the body cannot use pantothenic acid for forming ATP; additional to vitamin B5 loss, some expelling mechanism might exist in the diabetic condition such as impaired renal tubular reabsorption of the vitamin or impaired conversion of pantothenic acid into its active form (4). The thickening of the basement membrane, hypertrophy of glomerular structures, and accumulation of extracellular matrix components are the major findings in DN (3). Replacement of depleted vitamin B5 stores lead to an improvement in histological findings such as tubular dilatation, thickening of glomerular and tubular basement membranes probably reducing oxidative stress. DEX protective effect has been reported in different animal model and on variety of tissues including kidney (15), liver (8) and testicular ischemia (7) and these studies explained and supported by improvement of biochemical parameters such as glutathione and malondialdehyde levels. Restoration

of antioxidant defence system may help to improve inflammatory status, hence protects the kidney. Tutun et al. (16) publication also supports our findings that DEX protects the kidney from diabetes by increasing antioxidant activity.

It has been reported that increased infiltration of monocytes and macrophages and activated intrarenal lymphocytes in interstistitium are the underlying immunopathological mechanisms of DN (2,3). DEX treatment has been found effective to reduce caspases level to prevent apoptosis and significantly decreased tubular necrosis (15) in renal ischemia-reperfusion injury. Additionally, has demonstrated intravesical DEX application reduce the inflammatory leukocytes and mast cells infiltration in animal model of chemical cystitis (12). Immunohistochemistry staining is required for further research to understand treatment effects of DEX especially on cytokine pathway.

Conclusion

The STZ diabetes model produce kidney damage within 6 weeks and DEX treatment protects the tissue from damage, at some point by regulating the inflammatory responses and oxidant status. DEX is well-tolerated and highly safe adjuvant therapy for preventing diabetes induced complications in kidney.

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Ethics

Ethics Committee Approval: Aydın Adnan Menderes University Animal Ethics Committee's approval for the study (decision no: HEK/2009/64, date: 02.09.2009).

Informed Consent: The study is an animal experiment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.G.C., B.D., Design: N.G.Ç., B.D., Supervision: N.G.C., B.D., Fundings: N.G.Ç., K.G., B.D., Materials: M.A., M.Ak., Data Collection or Processing: N.G.C., K.G., M.A., M.Ak., Analysis or Interpretation: N.G.C., M.A., M.Ak., B.D., Literature Search: N.G.C., K.G., M.A., M.Ak., B.D., Critical Review: N.G.Ç., B.D., Writing: N.G.C., K.G., M.A., M.Ak., B.D.

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

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Original Article / Özgün Araştırma

Haematological Parameters in Children with Serum Folate Deficiency

Serum Folat Eksikliği Olan Çocuklarda Hematolojik Belirteçler

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Abstract

Objective: Folate deficiency is common globally, especially in low- and middle-income countries. The best-known morbid effects of folate deficiency are haematological in nature. This study aimed to identify the haematological parameters status of folate deficiency in children.

Materials and Methods: Data were gathered from the outpatient clinics electronic database of Gaziantep University Hospital. A total of 200 children were evaluated. The inclusion criteria were paediatric patients with folate deficiency (<4 ng/mL).

Results: Of the 200 children with folate deficiency, 46.5% showed low haemoglobin level (<11 g/dL), reflecting anaemia status. Macrocytic anaemia was detected in 13.5% of the patients. Thrombocytopaenia was detected in 20%, leukopenia in 17%, lymphopaenia in 6%, neutropenia in 5% and pancytopenia in 12% of the patients. Positive correlations were found between folate levels and haemoglobin ($r=0.18$; $p<0.01$), haematocrit ($r=0.17$; $p<0.05$), red blood cell ($r=0.19$; $p<0.01$), lymphocyte count ($r=0.20$; $p<0.01$) and platelet count ($r=0.15$; $p<0.05$). However, inverse correlations were found between folate level and red cell distribution width ($r=-0.18$; $p<0.01$), and no correlations were noted between folate level and mean corpuscular volume ($r=-0.72$; $p>0.05$).

Conclusion: Our data showed that these children not only develop anaemia but also leucopenia, thrombocytopenia and pancytopenia. Monitoring haematological parameters could be useful in children with folate deficiency.

Keywords
Folate, anemia, children

Anahtar Kelimeler
Folat, anemi, çocuklar

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Öz

Amaç: Folat eksikliği düşük ve orta gelirli ülkelerde yaygındır. Folat eksikliğinin en önemli morbid etkisi hematolojiktir. Bu çalışmanın amacı folat eksikliği olan çocuklarda hematolojik parametrelerin değerlendirilmesidir.

Gereç ve Yöntemler: Bu çalışmanın verileri Gaziantep Üniversitesi Hastanesi ayaktan hasta klinikleri elektronik veri sisteminden toplanmıştır. İki yüz çocuk hasta değerlendirilmiştir. Folat eksikliği olan çocuk hastalar çalışmaya dahil edilmiştir (<4 ng/mL).

Bulgular: Folat eksikliği olan 200 çocuk değerlendirilmiş olup, %46,5 hastada anemi mevcuttu. Bunların %13,5'inde makrositik anemi mevcuttu. Hastanın %20'sinde trombositopeni, %17'sinde lökopeni, %6'sında lenfopeni, %5'inde nötropeni, %12 hastada pansitopeni saptandı. Folat seviyesi ve hemoglobin ($r=0,18$), $p<0,01$, hematokrit ($r=0,17$), $p<0,05$, kırmızı küre ($r=0,19$), $p<0,01$, lenfosit sayısı ($r=0,20$), $p<0,01$ ve trombosit sayısı ($r=0,15$), $p<0,05$ arasında pozitif korelasyon mevcuttu, ancak folat seviyesi ve eritrosit dağılım genişliği ($r=0,18$), $p<0,01$ arasında ters ilişki mevcuttu. Ayrıca folat seviyesi ve ortalama eritrosit volümü ($r=-0,72$), $p>0,05$ arasında ilişki bulunamadı.

Sonuç: Bizim çalışmamıza göre folat eksikliği olan çocuklarda yalnızca anemi görülmemekte ayrıca lökopeni, trombositopeni ve pansitopeni de görülmektedir. Ayrıca folat eksikliği olan çocuklarda hematolojik parametrelerin takibi önemlidir.

Introduction

Folate deficiency (FD) is common in many parts of the world, especially in low and middle-income countries. It has become increasingly rare in countries where certain food groups have been supplemented with folate. Folate fortification of food in the developed countries has decreased the prevalence of FD to <1% of the population (1). Also, in countries where the supplementation of foods does not occur, FD is subsequently more frequent. Over the last three decades the prevalence of FD seems to have reduced from 70-75% to 2-10% as reported in various studies in children from different regions. Hovewer, prevalence of FD vary among different communities with different eating habits and socioeconomic levels (2,3).

The best-known morbid effects of FD are hematological. There is a large body of information, derived from studies of various populations, on the prevalence of folate FD as determined by biochemical assays, but it is uncertain how much of this apparent deficiency is translated into morbid hematological change (4). FD is manifest by macrocytic anemia resulting from megaloblastic change in the bone marrow. This form of abnormal hematopoiesis may lead to anemia, neutropenia, and thrombocytopenia (4). Also, changes in hematological parameters, such as hemoglobin (Hb), hematocrit (HTC), red blood cell (RBC), mean corpuscular volume (MCV), red cell distribution width (RDW), and mean platelet volume (MPV) in FD may be useful in diagnosis. Also, there is uncommon data about these parameters (5,6).

The present study evaluates the varying hematological manifestations in 200 children diagnosed as FD. In addition, we compared hematological parameters between FD with anemia (Hb<11 g/dL) and without anemia (Hb≥11 g/dL).

Materials and Methods

The data gathered from our institute Gaziantep University Hospital outpatient clinics electronic database. The period of this cross-sectional retrospective study was from 2019 to 2020. Two hundred children were evaluated: Ninety six females (48%) and 104 (52%) males. Ages of the patients were from 1 to 16 years old. The inclusion criteria were child patients with less than 4 ng/mL folate levels. The hematological parameters were measured using a Sysmex XN1000 analyzer. Serum folate levels were done by Beckman Coulter, UniCel DXI 800 Access immunoassay system on the same day as blood collection. Because it was a retrospective study, patient consent could not be obtained. The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep University (protocol no: 2020/81).

We used serum folate levels cutoff of <4 ng/mL for children to estimate FD since this was a widely used criterion in previous studies (7,8). Macrocytosis was defined as MCV of >85 fL (9). Anemia was defined as Hb levels less than 11 g/dL, thrombocytopenia platelet counts less than 150,000/mm^3 and leucopenia white blood cell (WBC) counts less than 4,000/mm^3 and lymphopenia levels as lymphocyte counts less than 1,500/mm^3 with neutropenia levels as absolute neutrophil counts less than 1,500/mm^3 for children in our study (9). Pancytopenia was defined as Hb levels <11 g/dL, WBC counts <4,000/mm^3, and platelet counts <150,000/mm^3. Their red cell indices [MCV, mean corpuscular Hb (MCH), mean corpuscular Hb concentration (MCHC), and RDW], were noted. This study group was divided into four groups as group 1, cases <3 ng/mL (n=63, 31.5%), and group 2, cases 3-4 ng/mL (n=137, 68.5%) according to folate levels, and group 3, cases <11 g/dL (n=93, 46.5%), and group 4, cases ≥11 g/dL (n=107, 53.5%) according to Hb levels.

Statistical Analysis

Data were analyzed using SPSS 23.0 software (SPSS, Inc., Chicago, IL, USA). Demographic data were shown as means and standard deviation (SD) or percentages. Categorical variables were compared by using chi-square test. Spearman's correlation analysis was performed to examine the correlations between age and folate, and hematological measures. Two-tailed significance values are reported throughout. A probability level of $p<0.05$ was used to indicate statistical significance.

Results

The sample consisted of 200 children with FD (104 males, 96 females) between 1 and 16 (mean ± SD =9.3±4.6) years. The male-female ratio was 1.08. Table 1 shows demographic characteristics of the subjects.

The mean ± SD of laboratory measures, including folate levels, and hematological parameters, are

summarized in Table 2. Anemia was detected in 93 patients (46.5%), anemia without macrocytosis in 66 (33%), anemia with macrocytosis in 27 (13.5%), thrombocytopenia in 40 (20%), leukopenia in 34 (17%), lymphopenia in 12 (6%), neutropenia in 10 (5%), and pancytopenia in 24 patients (12%). Leukopenia coexisted with anemia in 7 (3.5%) patients, leukopenia coexisted with thrombocytopenia in 4 (2%) patients, anemia coexisted with thrombocytopenia in 24 (12%) patients. Folate levels, Hb, HTC, RBC, and lymphocyte levels were significantly lower, and RDW levels was significantly higher in group 1 (folate levels <3 ng/mL). Hb, HTC, RBC, MCV, MCH, MCHC and neutrophil levels were significantly lower, and RDW and lymphocyte levels were significantly higher in group 3 (Hb levels <11 g/dL). There was no statistical significant difference between females and males in all measures.

An examination of the correlation, there were positive correlations between folate levels and, Hb, (r=0.18), p<0.01, HTC, (r=0.17), p<0.05, RBC, (r=0.19), p<0.01, lymphocyte, (r=0.20), p<0.01, and platelet levels (r=0.15), p<0.05, however there were inverse

Table 1. Demographic characteristics

	Total n=200	Group 1, folate levels <3 ng/mL (n=63)	Group 2, folate levels 3-4 ng/mL (n=137)	Group 3, hemoglobin levels <11 g/dL (n=93)	Group 4, hemoglobin levels ≥11 g/dL (n=107)
Age, years Mean ± standard deviation	9.3±4.6	9.2±4.5	9.4±4.8	7.3±4.5	11±4
Gender, n (%)					
Male	104 (52%)	29 (46%)	75 (54.7%)	49 (52.7%)	55 (51.4%)
Female	96 (48%)	34 (54%)	62 (45.3%)	44 (47.3%)	52 (48.6%)

Table 2. Folate, and hematological values

	Total n=200	Group 1, folate levels <3 ng/mL (n=63)	Group 2, folate levels 3-4 ng/mL (n=137)	p	Group 3, hemoglobin levels <11 g/dL (n=93)	Group 4, hemoglobin levels ≥11 g/dL (n=107)	p
Folate (ng/dL)	3.2±0.6	2.4±0.4	3.5±0.2	<0.05	3.1±0.6	3.3±0.5	>0.05
Hb (g/dL)	10.9±2.5	10.3±2.5	11.2±2.5	<0.05	8.6±1.5	12.9±1.2	<0.0001
RBC (/mm^3)	4.3±0.9	4±1	4.4±0.9	<0.05	3.6±1	4.8±0.5	<0.0001
HTC (%)	33.8±7.5	32.3±7.3	34.5±7.6	<0.05	27.5±5.8	39.3±3.4	<0.0001
MCV (fL)	80±10.1	81.2±10.7	79.4±9.9	>0.05	77.8±12.5	81.9±7	<0.05
MCH (pg)	25.8±4.3	26.1±4.5	26.7±4.2	>0.05	24.6±5.4	26.9±2.7	<0.05
MCHC (g/dL)	32.2±3.1	31.9±2.1	33.6±2.4	>0.05	31.6±4.3	32.8±1.2	<0.05
RDW (%)	16±3.6	17±4	15.5±3.4	>0.05	18.1±3.8	14.1±2.2	<0.0001
WBC (mm^3)	8055±4677	7460±4742	8329±4638	>0.05	7712±5306	8354±4053	>0.05
Lymphocyte (mm^3)	3185±2173	2782±2283	3370±2103	<0.05	3207±2692	3167±1604	>0.05
Neutrophile (mm^3)	3670±2588	3684±3029	3663±2370	>0.05	3284±2892	4006±2252	<0.05
Platelet (mm^3)	308.876±196.646	271.000±180.756	32.6291±201787	>0.05	301.547±248.971	315.243±136.783	>0.05
MPV (fL)	9.7±1	9.6±0.8	9.8±1.1	>0.05	9.6±1	9.9±1.1	>0.05

Hb: Hemoglobin, RBC: Red blood cell, HTC: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, WBC: White blood cell, MPV: Mean platelet volume, p<0.05 was accepted to be statistically significant

correlations between folate and RDW levels (r=-0.18), p<0.01. Moreover, there were no correlations between folate levels and, age (r=0.06), p>0.05, MCH (r=-0.48), p>0.05, MCHC (r=0.05), p>0.05, MCV (r=-0.72), p>0.05, MPV (r=0.008), p>0.05, and neutrophil levels (r=0.09), p>0.05.

Discussion

FD is usually due to insufficient dietary intake but can also originate from intestinal malabsorption, defect in folate metabolism. Serum folate concentration is a good indicator of dietary folate intake and the most widely used method for assessing status (10). FD is associated with hematologic abnormalities. Hematologic manifestations of FD include anemia, macrocytosis, leukopenia, thrombocytopenia and pancytopenia (4-6). In this study, we analysed the relationship between hematological status and FD.

Relatively few data on the frequency and diversity of hematologic abnormalities in childhood FD have been reported (4-6,11,12). Hematologic abnormalities of anemia has been frequently associated with FD, but thrombocytopenia, leucopenia, and pancytopenia are less frequently seen (4-6,13). In the present study, anemia was detected in 93 patients (46.5%), thrombocytopenia in 40 (20%), leukopenia in 34 (17%), lymphopenia in 12 (6%), neutropenia in 10 (5%), and pancytopenia in 24 patients (12%) (Table 2).

Folate is a carbon donor for pyrimidine and purine synthesis, which are needed for the rapidly developing erythroid cells. Impaired DNA synthesis, a result of FD, leads to erythroid cell apoptosis and anemia (14,15). In the Azimi et al. (16) study, serum folate had a significant positive correlation with RBC (r=0.271), Hb (r=0.279) and HTC (r=0.316) levels, but not with MCV levels. This shows that MCV levels are not a reliable marker for FD. They found that serum folate was inversely correlated with RDW and MPV, but this was not statistically significant. Another study, De Bruyn et al. (17) reported that for serum folate concentrations ≤5 ng/dL, a significant negative impact was noted on the RBC count, HTC and Hb levels. Ndiaye et al. (10) found that, mean Hb levels was 116.86 (1.18) g/L, and 47.63% of the women involved in the study were anemic. Also, a positive and significant correlation was found between Hb and serum folate levels (r=0.07; p=0.0167). In the study performed by Villalpando et al. (12) 14% of children had low erythrocyte folate levels and anemic children had significantly lower folate levels compared with non-anemic children. Silva et al. (11) analyzed the nutritional status of vitamin B_{12} and folate levels with anemia in 460 children. In their study, Hb levels was positively associated with serum folate levels. In our study there were positive correlations between folate levels and, Hb, (r=0.18, p<0.01), HTC, (r=0.17, p<0.05), RBC levels, (r=0.19, p<0.01), however there were inverse correlations between folate and RDW levels (r=-0.18, p<0.01) but not with MCV (r=-0.72, p>0.05), MCH (r=-0.48, p>0.05), MCHC (r=0.05, p>0.05), and MPV levels (r=0.008, p>0.05). Our finding of a positive association between Hb concentration and folate status is consistent with reports from other studies conducted.

Folate are required in the synthesis of nucleoproteins and deficiency results in defective synthesis of DNA and RNA (18). Thrombocytopenia is believed to be due to impaired DNA synthesis resulting in ineffective thrombopoiesis. Isolated thrombocytopenia is a common indication for hematologic consultation. Testing for folate deficiencies is commonly performed during the evaluation of cytopenias. In the series by Erkurt et al. (19) 5% of the patients admitting with thrombocytopenia had megaloblastic anaemia. Another study, Gupta et al. (13) analyzed the varying clinico-hematological manifestations in 50 children diagnosed as megaloblastic anemia over a four year period. Thrombocytopenia was reported in 30% cases and leucopenia in 14% cases in the study. In the Dhoriya et al. (20) study, found that mean Hb, WBC and platelets in 59 patients of megaloblastic anemia were 6.6 g/dL, 2,800/mm^3 and 57,492/mm^3 respectively. In our study thrombocytopenia was detected in 40 (20%), leukopenia in 34 (17%), lymphopenia in 12 (6%), neutropenia in 10 (5%). Cytopenias is believed to be due to impaired DNA synthesis resulting in ineffective leukopoiesis and thrombopoiesis.

Pancytopenia is simultaneous presence of thrombocytopenia, leukopenia and anemia. Ineffective leukopoiesis, thrombopoiesis and erythropoiesis resulting from programmed cell death in the absence of folate, and reduced survival of precursors in peripheral blood are causes of pancytopenia in FD anemia (21). There is a little study in which micronutrients especially folate and

vitamin B_{12} are associated with pancytopenia (22,23). In our study of children with FD 24 patients (12%), had pancytopenia. Talarmin et al. (24) recognized that vitamin B_{12} and folate deficiencies are common in underdeveloped countries and are responsible of megaloblastic anemia and pancytopenia. In the Sarode et al. (25) study found that out of 139 patients of pancytopenia, 102 cases in whom the biochemical parameters were available, vitamin B_{12} deficiency was detected in 76%, FD in 6.8%, combined B_{12} and folate deficiency in 8.8%; the remaining 7.8% had normal vitamin levels at presentation. A hundred nine pediatric patients with pancytopenia were analyzed by Bhatnagar et al. (23) retrospectively and megaloblastic anemia was found to be the most common etiological factor (28.4%). Gomber et al. (26) in their study reported an incidence of 11% while Mukiibi et al. (27) had 47% cases of megaloblastic anemia presenting as pancytopenia. In the Gupta et al. (13) study, of the 50 children with megaloblastic anemia, 43.8% were presenting as pancytopenia.

Limitations of the retrospective study are the small sample size and the lack of analysis of other variables that reflect the tissue deficiency of folate such as serum homocysteine. Further, this study did not collect any data about the medical history, iron and vitamin B_{12} status of the population. In addition, we did not evaluate the dietary intake of folate to better assess the folate status of participants. Our results reflect an outpatient population, and it is not representative of general population.

Conclusion

Hematologic abnormalities accompanying FD are common. Here, in the present study, our results emphasize that FD should be considered in a children with hematologic abnormalities such as anemia without macrocytosis, anemia with macrocytosis, leukopenia, thrombocytopenia, or pancytopenia, especially in developing geographical areas.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Gaziantep University (protocol no: 2020/81).

Informed Consent: Because it was a retrospective study, patient consent could not be obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.T.A., Design: H.T.A., Supervision: H.T.A., M.Ö., Fundings: H.T.A., M.Ö., Materials: M.Ö., Data Collection or Processing: M.Ö., Analysis or Interpretation: H.T.A., Literature Search: H.T.A., Critical Review: H.T.A., Writing: H.T.A., M.Ö.

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

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Original Article / Özgün Araştırma

Clinical and Laboratory Findings of Paediatric Patients with Brucellosis

Çocukluk Çağı Bruselloz Hastalarının Klinik ve Laboratuvar Bulguları

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Abstract

Objective: Brucellosis is the most common bacterial zoonotic disease transmitted via unpasteurised milk and dairy products from infected animals. This study aimed to evaluate paediatric patients treated for brucellosis and followed for 2 years.

Materials and Methods: The records of 73 patients with childhood brucellosis who had undergone treatment and follow-up for 2 years were retrospectively evaluated.

Results: The patient age ranged from 1 to 14 years, with 39 boys (53%) and 34 girls (47%). Fever (94%) was the first common symptom. Other symptoms, in the order of frequency, were myalgia (80%), arthralgia (75%), fatigue (38%) and anorexia (33%). Complications included sacroiliitis (12%), hemophagocytic lymphohistiocytosis (4%), epididymo-orchitis (1.3%), focal abscess (1.3%) and meningitis (1.3%). Splenomegaly, hepatomegaly and lymphadenopathy (24%, 33% and 5%, respectively) were also reported. Moreover, 18% of the patients had hepatosplenomegaly at initial admission. Dermatological involvement revealed maculopapular rash in 4.1% and petechial rash in 9.6% of patients. Body weight loss was observed in 14% of the cases. In addition, 76.3% and 23.7% of the patients had acute and sub-acute forms, respectively.

Conclusion: Brucellosis can display several different clinical presentations. This diversity can lead to diagnostic delay. In settlements where the disease is common, patients with fever and joint pain should be treated early and the disease should be ruled out.

Keywords
Brucellosis, childhood, clinical characteristics, epidemiology

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Bruselloz, çocukluk çağı, klinik özellikler, epidemiyoloji

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Öz

Amaç: Bruselloz, enfekte hayvanlardan pastörize edilmemiş süt ve süt ürünleriyle bulaşan en yaygın bakteriyel zoonotik hastalıktır. Bu çalışmada bruselloz tedavisi gören ve 2 yıl boyunca takip edilen pediatrik hastaların değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Çocukluk çağı brusellozlu olan 73 hastanın 2 yıllık süredeki tedavi ve takip kayıtları geriye dönük olarak incelendi.

Bulgular: Yaşları 4-14 arasında değişen 73 hastanın 39'u erkek (%53) ve 34'ü kız (%47) idi. En sık görülen semptomlar ateş (%94), artralji (%75), miyalji (%80), yorgunluk (%38) ve iştahsızlık (%33) idi. Komplikasyon olarak sakroileit (%12) ve hemofagositik lenfohistiyositoz (%4) saptandı ve diğer yaygın komplikasyonlar epididimoorşit (%1,3), fokal apse (%1,3) ve menenjit (%1,3) idi. Splenomegali, hepatomegali ve lenfadenopati sıklıkları sırasıyla %24, %33 ve %5 idi. Çalışmaya alınan olguların %18'inde tanı anında hepatosplenomegali varlığı saptanmıştır. Dermatolojik tutulum üçünde makülopapüler döküntü, yedisinde peteşiyal döküntü

şeklindeydi. Olguların %14'ünde kilo kaybı tespit edildi. Akut form %76,3 hastada mevcutken subakut form %23,7 hastada mevcuttu. **Sonuç:** Bruselloz çok farklı klinik tablolarla ortaya çıkabilir. Hastalığın spektrumundaki bu çeşitlilik tanıda gecikmelere yol açabilir. Hastalığın sık görüldüğü yerleşim yerlerinde ateş ve eklem ağrısı olan hastalarda öncelikli olarak düşünülmeli ve hastalık ekarte edilmelidir.

Introduction

Brucellosis continues to be an important public health problem in many developing countries. Brucellosis can be seen at any age. Childhood cases constitute 20% to 25% of brucellosis cases (1). The disease agent is immobile, small, gram negative coccobacillus (2). *Brucella abortus, Brucella melitensis, Brucella suis* and *Brucella canis* are species pathogenic to humans (3). More than 500,000 new cases are reported worldwide each year. In some endemic countries the prevalence is greater than 10/100,000 (4). Animals and their products are sources of brucellosis contamination. Transmission is usually through direct contact of the infected animal's secretions with disintegrated skin or mucosa, use of unpasteurized milk and dairy products, inhalation of infected aerosols and contact with the conjunctiva. Brucellosis may present with a wide variety of signs and symptoms, multisystem involvement such as cardiovascular, skeleton, neural, skin and intestinal system. Brucellosis is a benign disease that often responds well to treatment, however; involvement in the bone, cardiovascular and nervous system can cause significant illness and death (5). Transmission through consumption of unpasteurized milk and dairy products is the most common route of transmission. The frequent clinical symptoms and signs of the disease are high fever, myalgia, arthralgia, sweating, weakness, and splenomegaly. Weight loss, arthritis, vomiting, abdominal pain, headache, cough may be seen (3). A definitive diagnosis is made by isolating *Brucella* spp. from blood, bone marrow or other tissue cultures, body fluids such as cerebrospinal fluid (4-6). However, the commonly used diagnostic method is serum agglutination test, which reveals IgG and IgM type *Brucella* spp. antibodies. A single serum brucella titer of 1:160 or above is considered to support the diagnosis (7,8). Here, we retrospectively evaluated 73 brucellosis cases who applied to the General Pediatric Outpatient Clinic and Pediatric Emergency Outpatient Clinic between August 2018 and December 2019.

Materials and Methods

In this study, 73 brucellosis cases who applied to Van Yüzüncü Yıl University, Faculty of Medicine Hospital Pediatrics General Pediatric Outpatient Clinic and Pediatric Emergency Outpatient Clinic between December 2017 and December 2019 were evaluated retrospectively. Diagnosis of the disease was made by positive brucella agglutination titers (titers 1:160 or higher) or isolation of the causative agent in the presence of clinical findings consistent with brucellosis. The cases were grouped according to the duration of symptoms as acute (0-2 months), subacute (2-12 months) and chronic (>12 months) (6). The available data of the cases in the study were obtained from electronic medical records and files. Patients with recurrent disease were interviewed by phone and confirmed. Recurrence of disease was defined as recurrence of symptoms within 6 months of treatment or a positive blood culture (9). Patients age, gender, city of residence, season at the time of admission and whether there was a family history of similar disease were recorded. The first admission clinical symptoms and examination findings of the patients and the treatments given were evaluated. Necessary imaging methods (direct radiography, magnetic resonance, ultrasonography imaging) were used in cases with suspected complicated brucellosis. Since bone marrow aspiration was performed in cases with suspicion of pancytopenia and hemophagocytic lymphohistiocytosis as hematological involvement, the available data were recorded. The presence of neurobrucellosis was investigated by lumbar puncture performed in patients diagnosed with brucellosis, with headache, seizures, impaired consciousness, and vomiting. The presence of neurobrucellosis was detected by the presence of Wright agglutination titer in the cerebrospinal fluid, the presence of lymphocytic

pleocytosis, protein increase, low glucose level and positive detection in the standard tube agglutination test. Informed consent forms were collected from the parents of the patients.

Ethics

The study was initiated after being approved by the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (decision no: 2020/06-04, date: 18.09.2020). All analyzes were carried out in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

The analysis of the data was done with the SPSS 13.0 package program. Descriptive statistics are results for continuous and sortable variables as mean ± standard deviation, median (maximum-minimum); categorical variables were expressed as "%".

Results

The ages of the patients ranged from 1 to 14 years, with 39 boys (53%) and 34 girls (47%). The mean age of the subjects included in the study was 10.2 years (±3.4). The characteristics and clinical findings of the patients are shown in Table 1. Sixty six cases (90.6) had a history of consuming unpasteurized milk and dairy products. In 28 (38%) cases, there was a history of both contact with animals and eating fresh cheese. Consumption of unpasteurized milk or dairy products was significantly common in 21 cases with a family history of brucellosis. The disease was more common in those residing in rural areas. The most frequent symptoms were fever (94%), arthralgia (75%), myalgia (80%), fatigue (38%), and anorexia (33%). When evaluated in terms of complications, it was determined as sacroileitis (12%) and Hemophagocytic lymphohistiocytosis (4%), epididymoorchitis (1.3%), focal abscess (1.3%) and meningitis (1.3%), respectively (Table 1). Neurobrucellosis was detected in only 1 of the cases, but the agent could not be isolated in the cerebrospinal fluid culture. This patient was diagnosed with a positivity of agglutination titer in the cerebrospinal fluid. The frequencies of splenomegaly, hepatomegaly and lymphadenopathy were 24, 33, and 5%, respectively. The presence of hepatosplenomegaly at the time of diagnosis was found in 18% of the cases included in the study. Dermatological involvement was maculopapular rash in three of them, and petechial rash in seven. Body weight loss was detected in 14% of the cases. Of the patients in the study, 76.3% had acute form and 23.7% had subacute form. Table 2 shows the results of the Laboratory examinations. The diagnosis of brucellosis was made using the standard tube agglutination test in all cases included in the study. All of these cases

Table 1. Clinical characteristics and complications of patients with brucellosis

Variable	n (%)
Age at diagnosis, mean	10.2±3.4
Gender	
Male	43 (58)
Female	30 (32)
Consumption of raw or unpasteurized milk and milk products	66 (90.6)
Family history in terms of brucellosis	21 (28)
Symptoms	
Myalgia	59 (80)
Arthralgia	54 (75)
Anorexia	24 (33)
Fever	69 (94)
Fatigue	27 (38)
Abdominal pain	5 (6)
Headache	10 (14)
Signs	
Splenomegaly at diagnosis	17 (24)
Hepatomegaly at diagnosis	24 (33)
Arthritis	21 (29)
Weight loss	10 (14)
Petechiae	7 (10)
Hepatosplenomegaly at diagnosis	13 (18)
Lymphadenopathy	4 (5)
Clinical diagnosis	
Acute	76.3
Subacute	23.7
Chronic	0
Complications	
Meningitis	1 (1.3)
Epididymo-orchitis	1 (1.3)
Focal abscess	1 (1.3)
Sacroileite	9 (12)
Haemophagocytic lympho histiocytosis	3 (4)

had titres of 1:160 or more. *Brucella melitensis* was isolated in only 17 of the cases whose blood culture was studied. While bone marrow aspiration was performed in 7 patients with pancytopenia, bone marrow culture was studied. Culture positivity was detected in 4 out of 7 cases whose bone marrow culture was studied. It was observed that C-reactive protein (CRP) value increased in 41 cases (56%). Although the sedimentation rate was 20-40 mm/h in 41 cases, values above 40 mm/h were found in 5 cases. Anemia was detected in 31 (42%) patients and thrombocytopenia in 11 patients (15%). Leukopenia was found in 17% of the patients, and leukocytosis in 19%. High liver enzymes were found in 49% of 36 cases (Table 2). Oral rifampicin (15-20 mg/kg/day), oral doxycycline (4 mg/kg/day) in patients over 8 years of age; oral rifampicin (15-20 mg/kg/day) and oral trimethoprim-sulfamethoxazole (10-12 mg/kg/day) were given to cases under 8 years of age. The case we detected neurobrucellosis combined treatment with gentamicin (5 mg/kg/day), rifampicin (20 mg/kg/day) and ceftriaxone (100 mg/kg/day) was given. Antibiotic treatment was given for 6 weeks, 4 months in sacroileitis cases and 6 months in meningoencephalitis cases. Except for minor gastrointestinal system complaints (nausea, abdominal pain) related to the treatments, no serious side-effects were observed. Recurrence of the disease developed in 4 patients who were given doxycycline and rifampin as treatment. No recurrence was detected after 6 weeks of the same treatment regimen given to these recurrent cases.

Table 2. Laboratory findings of patients with brucellosis

Variable	n (%)
Anemia (Hgb <12 g/dL)	31 (42)
Leukopenia (4x10^3/mL)	13 (17)
Thrombocytopenia (<150x10^3/mL)	11 (15)
Pancytopenia	7 (9)
Leukocytosis (>10.5x10^3/mL)	14 (19)
Thrombocytosis (>450x10^3/mL)	6 (8)
Elevated aminotransferases (>40 U/L)	36 (49)
ESR (20-40 mm/h)	41 (56)
ESR (>40 mm/h)	5 (6)
Elevated CRP (>5 mg/dL)	41 (56)
Culture positive	21 (28)

Hgb: Hemoglobin, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Discussion

Brucellosis is still an important public health problem in our country. It is noticed that this problem is more common in Van than in other cities. The most important reason for its prevalence in regions such as the east and southeast is the prevalence of raw milk and dairy products, nutrition and livestock (10). In our current study, 90.6% of the cases had a history of feeding with raw milk and dairy products, while a history of animal husbandry was found in 53% of the cases. There was a family history in 28% of our cases. In one study, 80.4% of the cases had consumption of raw milk and dairy products, and 33% had a family history (11). In other studies reported in the literature, consumption of unpasteurized milk and dairy products was reported between 62.4% and 94.6% (9,12,13). In the study conducted by Tanir et al. (14), 15.6% of patients with brucellosis had a family history. It was determined from the anamnesis that some patients had past and current cases of brucellosis among their family members. There were no clinical signs of symptomatic infection in all cases. In this study, it was reported that brucellosis is common among other family members and needs attention (15). Therefore, screening family members is essential when a patient with brucellosis is diagnosed. Although standard tube agglutination test is mostly positive in acute cases, seropositivity may occur after a few weeks in some cases. Seropositivity sap 1/160 was found in all of our patients. *Brucella* spp. was isolated from the blood culture of 17 cases and from both the blood and bone marrow cultures of 4 cases. The agent could be isolated in only 4 of 7 patients whose bone marrow culture was studied. The definitive diagnosis is based on isolation of the agent from different samples such as bone marrow and blood (16). Different rates have been reported for blood culture positivity. Culture positivity rates in the range of brucellosis in Turkey is between 12-70%. These rates may be affected by reasons such as not storing the culture samples for a long time and the patient's previous use of antibiotics (17). Blood culture positivity was found to be 28% in our series. This rate can be considered low. We think that this may be due to the previous antibiotic use of our cases. In a study, 83.5% of the cases were evaluated as acute, 8.9% as subacute and 7.6% as chronic brucellosis (18). In another study, the acute

form, chronic form and subacute form were found to be 75.3%, 23.7%, and 1%, respectively (11). In our study, 76.3% of the patients had acute form and 23.7% had subacute form.

Brucellosis can present with a different of symptoms and signs that are not specific and can be confused with many diseases (8). In the literature, fever and joint complaints are the most common clinical findings and were reported as 41-85% and 73-91%, respectively (6,19-21). In one study, osteoarticular involvement was the most common (59.6%), lymphadenopathy (42.1%), hepatomegaly (33.3%), splenomegaly (33.3%) and peripheral nerve involvement (3.5%) (22). 75% of our patients had arthralgia, 94% had fever and 29% had arthritis. The liver is the largest organ of the reticuloendothelial system that is why it can almost always be involved and liver function tests may increase. Tanir et al. (14) reported that, when the examination findings were evaluated, hepatomegaly was observed in 15.6% of the patients, splenomegaly in 11.1% and hepatosplenomegaly in 6.7%, while lymphadenopathy was not detected in any patient. In our study, 33% of the cases had hepatomegaly, 24% had splenomegaly and 18% had hepatosplenomegaly, while lymphadenopathy was detected in 5%.

Laboratory findings in brucellosis are variable, and the elevation of erythrocyte sedimentation rate (ESR) and CRP was found in 40.8-81.1% and 50-87.2%, respectively (17,23-25) of the patients. The data determined in this study are also compatible with the literature, and the elevation of ESR and CRP was found to be 62% and 56%, respectively. Serum transaminase elevation in brucellosis has been reported at a rate of 25-60% (26), and it was found to be 49% similarly in our study. There are few studies in the literature on hematological complications associated with brucellosis in children compared to adults (27). Mild anemia and low white blood cell count are more common than pancytopenia and thrombocytopenia in hematological complications due to brucellosis (28). In a study, the rate of anemia in childhood brucellosis was reported between 20.4% and 53% (11,29). Thrombocytopenia is reported in 1% to 26% in a children series with brucellosis (27-30). Leukopenia has been reported (13.9%) in a children with brucellosis (27). In our study, similar to the previously reported studies, anemia was detected in 42% of our patients, thrombocytopenia in 15% and leukopenia in 17%. When we examined the literature, we found that the hematological involvement in brucellosis patients ranged from 3% to 21% with pancytopenia (27,28). We detected pancytopenia in 7 of our cases. Three patients with pancytopenia had hemophagocytic lymphohistiocytosis syndrome. In these patients, in addition to fever, hepatosplenomegaly, hepatitis, hypofibrinogenemia, and hyponatemia, ferritin values were above 500 mg/dL. There was evidence of hemophagocytosis in the evaluation of bone marrow aspiration of these patients with hemophagocytic lymphohisitiocytosis. With brucellosis treatment, the picture of these three patients resulted in complete recovery. Hematological, osteoarthricular, respiratory and cutaneous complications are more prominent in children. Neurobrucellosis, which is a rare complication, can be suspected due to its clinical features. Neurobrucellosis presents with avariety of clinical manifestations, and the symptoms are sometimes atypical. In our patient with neurobrucellosis, a continuous sleepiness was present in addition to weakness and fever. During the day, he slept an average of 17 hours before the treatment started. After the treatment of neurobrucellosis was started, his clinical findings improved rapidly.

Conclusion

As a result, brucellosis should definitely be considered in the differential diagnosis of patients who present with nonspecific complaints such as fever, arthralgia, weakness, and hepatosplenomegaly in endemic areas and who have cytopenia and high acute phase reactants in their examinations. Contamination should be prevented with measures such as frequent veterinary studies, identifying and treating sick animals, and increasing animal controls.

Ethics

Ethics Committee Approval: The study was initiated after being approved by the Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (decision no: 2020/06-04, date: 18.09.2020). All analyzes were carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent forms were collected from the parents of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.K., O.T., B.S., Design: S.K., M.B., Supervision: E.Ç.B., S.K., Fundings: E.Ç.B., S.K., Materials: S.K., K.K., Data Collection or Processing: M.B., O.T., Analysis or Interpretation: S.K., B.S., K.K., Literature Search: S.K., Critical Review: O.T., K.K., Writing: M.B., S.K.

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Original Article / Özgün Araştırma

Examination of the Knowledge Levels, Attitudes and Anxiety Sources Regarding Coronavirus Disease-2019 Infection in Dentistry Students in Clinical Practice

Klinik Uygulama Yapan Diş Hekimliği Fakültesi Öğrencilerinin Koronavirüs Hastalığı-2019 ile İlgili Bilgi Düzeylerinin, Tutumlarının ve Kaygı Kaynaklarının İncelenmesi

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Abstract

Objective: This study aimed to examine and evaluate the knowledge levels, attitudes and anxiety sources regarding coronavirus disease-2019 (COVID-19) infection in dentistry students in clinical practice.

Materials and Methods: Fourth- and fifth-year dentistry students of Aydın Adnan Menderes University and Akdeniz University were selected for this study. For data collection, a questionnaire survey was performed. The questionnaire contained 34 items on demographic data, knowledge level about COVID-19 infection and attitudes and anxiety sources about their education. Descriptive statistical methods and the Pearson chi-square test were used to analyse data. $P<0.05$ was statistically significant.

Results: A total of 137 students, including 75 females (54.7%) and 62 males (45.3%), participated in the study. Significantly higher levels of negativity and anxiety due to COVID-19 was found in female participants than in male participants, based on their responses to the following questions: "Do you believe that the lack of face-to-face training due to COVID-19 will negatively affect your working life?"; "Do you worry about graduating having completed clinical practice without direct patient care?"; "Do you worry about practising your job because of the coronavirus?" and the p values were found 0.019, 0.002 and 0.009, respectively. The answers for these questions were not related to the graduation degree.

Conclusion: The results reveal that female students demonstrated higher stress levels than male students based on the responses to some questions. Moreover, responses to the same questions were not related to the graduation degree. Further larger studies will give more accurate outcomes.

Öz

Amaç: Bu çalışmada yazarlar, klinik uygulama yapan diş hekimliği fakültesi öğrencilerinin koronavirüs hastalığı-2019 (COVID-19) enfeksiyonu ile ilgili bilgi düzeylerini, tutumlarını ve kaygı kaynaklarını incelemeyi ve değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntemler: Aydın Adnan Menderes Üniversitesi ile Akdeniz Üniversitesi, Diş Hekimliği Fakülteleri dördüncü ve beşinci sınıf öğrencileri bu çalışma için seçildi. Veri toplamak için bir anket kullanıldı ve bu anket demografik sorular, COVID-19 hakkında bilgi seviyesi soruları ve eğitim sürecindeki kaygı kaynakları ve tutum ile ilgili 34 sorudan oluşmaktaydı. Veriler, tanımlayıcı istatistiksel yöntemler ve Pearson ki-kare testi kullanılarak analiz edildi, p<0,05 istatistiksel olarak anlamlı kabul edildi.
Bulgular: Çalışmaya, 75 kadın (%54,7), 62 erkek (%45,3) olmak üzere toplam 137 katılımcı dahil edildi. Kadınların COVID-19 nedeniyle yaşadıkları olumsuzluklar ve anksiyete, "COVID-19 sebebiyle yüz yüze eğitimin yapılamamasının çalışma hayatına geçince olumsuz etkileri olacağına inanıyor musunuz?", "Doğrudan hasta bakımı olmadan klinik uygulamaları tamamlayarak mezun olmaktan endişe duyuyor musunuz?", "Koronavirüs sebebiyle mesleğinizi uygulamaktan endişe duyuyor musunuz?" sorularında erkeklerden istatistiksel olarak anlamlı derecede yüksek ve p değerleri sırasıyla 0,019, 0,002 ve 0,009 olarak bulundu. Aynı sorulara verilen cevapların mezuniyet derecesi ile ilişkisi bulunmadı.
Sonuç: Bazı sorulara verilen cevaplara göre kız öğrencilerin erkek öğrencilere göre daha stresli olduğu görüldü. Öte yandan aynı sorulara verilen cevapların mezuniyet derecesi ile ilgili olmadığı görüldü. Daha geniş kapsamlı çalışmalar konu ile ilgili daha detaylı bilgiler edinmemizi sağlayacaktır.

Introduction

A new outbreak of coronavirus occurred in December 2019 in Wuhan and quickly spread across China and other states in the world. Patients who presented at the hospital in Wuhan, China in mid-December of 2019 with headache, fever, dry cough, shortness of breath, and weakness were previously considered to be atypical pneumonia cases. However, some patients developed complications, such as respiratory failure, as the disease progressed and ventilation support was needed (1).

When the first case of such pneumonia was detected on December 12, influenza, other coronaviruses, and other diseases were excluded by laboratory tests, and on January 7, 2020, it was announced that a newly discovered coronavirus strain was isolated in these patients. On January 12, 2020, this virus was named as the 2019 novel coronavirus. The pneumonia caused by the new coronavirus was named by the World Health Organization (WHO) as coronavirus disease-2019 (COVID-19) on February 11, 2020, and this virus was renamed by the International Taxonomy Committee of Viruses [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)] (2). Previously, there have been outbreaks of coronavirus that have threatened public health, such as Middle East respiratory syndrome-CoV and SARS-CoV (3).

Coronaviruses are RNA viruses known to cause hepatic, respiratory, and neurological disorders (4). Unlike other enveloped viruses, the envelope of the coronavirus is derived from the host cell endoplasmic reticulum. This difference may be a factor that increases pathogenicity (5).

The spread and consequences of the outbreak have affected the whole population, causing widespread public health concerns. Faculty of dentistry students are also indirectly or directly associated with such outbreaks. If adequate precautions are not taken, the environments in which dentists work can potentially cause cross-contamination. Therefore, they need to know more and gain a better insight into such diseases. After the first COVID-19 case was detected in Turkey in March 2020, face-to-face education was interrupted in all universities, and clinical training was also suspended in addition to face-to-face education in departments such as dentistry and medicine. While theoretical education continued on the e-learning platform of the universities, clinical training could not be continued with conventional methods in these departments. Universities regulated the clinical training activities into the presentation of case reports, interactive-learning tutorials on the basis of clinical cases, and studying scientific articles. Even though clinical training has continued with different activities on the e-learning platform, these activities cannot replace direct patient care. This lacking of clinical training is planned to be recovered in the following semester.

In this study, the authors aimed to examine and evaluate the knowledge levels, attitudes and anxiety sources regarding the infection of COVID-19 of the dentistry faculty students who perform the clinical practice.

Materials and Methods

This descriptive study was performed with students of Aydın Adnan Menderes University,

Faculty of Dentistry and Akdeniz University, Faculty of Dentistry, nearly five months after the outbreak of the pandemic in Turkey, between July 15 and August 15, 2020. This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, Akdeniz University (decision no: KAEK-582, date: 22.07.2020), and the study was carried out in accordance with the ethical rules of the Declaration of Helsinki.

Data collection was done using a questionnaire, which was designed by the authors for this purpose through the "Google Forms" website. Fourth- and fifth-grade students, for whom face-to-face and clinical education including direct patient care have been interrupted under the COVID-19 pandemic, were chosen for this study and the students were informed about the survey. The questionnaire was delivered to the students via the smartphone application "WhatsApp" and there was an informative text about the study at the top of the questionnaire. In addition, beneath the informative text, there was a check box for the participants to agree to voluntarily participate in the study. The survey consists of 34 questions and three sections: 1) Demographic questions; 2) knowledge level questions about infection of COVID-19; and 3) questions related to attitudes and anxiety sources regarding their education/professional choices. The students who volunteered and answered all questions in both universities were included in the study.

Statistical Analysis

The data were statistically analysed using the Statistical Package for the Social Sciences (SPSS) software (version 23.0, SPSS Chicago, USA). The data were expressed as number, mean ± standard deviation, and percentage. Descriptive statistical methods and the Pearson chi-square test were used in the analysis of the data.

Results

A total of 137 participants, including 75 females (54.7%), 62 males (45.3%) were included in the study. Participants were between 21 and 29 years old, with a mean age of 22.89±1.1 years. Sixty-six (48.2%) of the participants were studying at Aydın Adnan Menderes University, Faculty of Dentistry and 71 (51.8%) at Akdeniz University, Faculty of Dentistry. Fifty-six (40.9%) of the participants were fourth-grade students and 81 (59.1%) were in the fifth grade.

The distribution of the answers given by the participants to the questions evaluating their knowledge level of COVID-19 is shown in Table 1. According to Table 1, all participants said "true" to the following statements: "The common symptoms of COVID-19 infection include cough, fever, and

Table 1. The distribution of the answers given by the participants to the questions evaluating knowledge level about coronavirus disease-2019

	True (n/%)	False (n/%)	Undecided (n/%)
COVID-19 is a viral infection	135/98.5	0/0	2/1.5
COVID-19 is transmitted through close contact with an infected person or animal	118/86.1	12/8.8	7/5.1
The common symptoms of COVID-19 infection include cough, fever, and shortness of breath	137/100	0/0	0/0
Headaches, muscle pain, loss of taste or smell are other symptoms of COVID-19	130/94.9	2/1.5	5/3.6
Antibiotics are the first step of the treatment	17/12.4	95/69.3	25/18.2
Washing hands with soap and water helps prevent disease transmission	136/99.3	1/0.7	0/0
Individuals with chronic diseases are more at risk for complications than healty individuals	137/100	0/0	0/0
Healthcare workers are more at risk than other workers	137/100	0/0	0/0
Transmission of the virus can be prevented by following the isolation rules given by the World Health Organization	117/85.4	6/4.4	14/10.2
The prevalence of COVID-19 can be reduced by the active participation of healthcare professionals in regular infection control programs	119/86.9	4/2.9	14/10.2

n: Number of participants, COVID-19: Coronavirus disease-2019

shortness of breath"; "Individuals with chronic diseases are more at risk of complications than healthy individuals"; and "Health-care workers are more at risk than other workers".

To the question "If the COVID-19 vaccine was available, would you use it?", 102 (74.5%) participants answered "yes", 5 participants (3.6%) answered "no" and 30 participants (21.9%) answered "undecided". To the question "Are you concerned about someone in your family being infected?", 127 (92.7%) participants answered "yes", 9 participants (6.6%) answered "no" and 1 participant (0.7%) answered "undecided".

The answers were distributed to the question "What is your source of information about the pandemic?" can be seen in Table 2.

To the question "What are you most afraid of about the pandemic?", 21 (15.3%) participants answered "being infected" and 116 participants (84.7%) answered "infecting other people".

The distribution of the answers given by the participants to the questions evaluating their attitudes and anxiety sources regarding COVID-19 infection is shown in Table 3. The answers given to the following questions have a relationship with gender, and p values are 0.041, 0.019, 0.002 and 0.009, respectively: "Considering we need to get used to living with viruses, are you hesitant about the choice of the department of speciality?"; "Do you believe that the lack of face-to-face training due to COVID-19 will have negative effects when it comes to your working life?";

Table 2. The distribution of the answers given to the question "What is your source of information about the pandemic?"

	n	%
The Health Ministry website	88	17.4
The World Health Organization website	48	9.5
Social media (Health Ministry, scientific board members etc.)	118	23.3
Social media (friends or health workers)	67	13.2
Television	90	17.8
Newspaper	34	6.7
Scientific publication/article	61	12.1
Total	506	100

Because there are multiple responses, the number of participants exceeds the sample size, n: Number of participants

Table 3. The distribution of the answers given by the participants to the questions evaluating their attitude and anxiety about their education/work life

	Yes (n/%)	No (n/%)	Undecided (n/%)
Do you believe that the lack of face-to-face training due to COVID-19 will have negative effects when it comes to your working life?	96/70.1	21/15.3	20/14.6
Do you believe that the lack of pratical training due to COVID-19 will have negative effects when it comes to working life?	117/85.4	10/7.3	10/7.3
Do you worry about clinical practice may be disrupted if the second wave of COVID-19 occurs?	116/84.7	13/9.5	8/5.8
Do you worry about graduating having completed clinical practices without direct patient care?	112/81.8	15/10.9	10/7.3
Do you think the distance education cause lack of teorical education in this period?	85/62	42/3 0.7	10/7.3
Do you think dentists are in the risk group for COVID-19?	133/97.1	3/2.2	1/0.7
Considering we need to get used to living with viruses, are you hesitant about the choice of the department of speciality?	26/19	95/69.3	16/11.7
Do you worry about practising your job because of the coronavirus?	85/62	36/26.3	16/11.7

n: Number of participants, COVID-19: Coronavirus disease-2019

"Do you worry about graduating having completed clinical practices without direct patient care?"; "Do you worry about practising your job because of the coronavirus?". On the other hand, the answers given to the same questions are not related to the graduation degree, and p values are 0.522, 0.9, 0.599, and 0.822, respectively.

A total of 114 (83.2%) of the participants knew about COVID-19 precautions in clinical practice and 110 (80.3%) of the participants had not received any training regarding COVID-19.

Discussion

Despite the efforts of health-care organizations, the COVID-19 pandemic is still increasing due to the difficulty in containing infection and the spread type of the infection (6). Dental students, dentists, and assistant staff are more exposed to pathogens which are transmitted through blood, saliva, or other body fluids than the normal population (7). For this reason, the knowledge and attitudes of students performing clinical practices about infectious diseases are very important (8).

Several studies are investigating the attitudes of dental students and knowledge levels about infectious diseases (7,9-13). As a very new disease, COVID-19 spreads fast and the information about it is limited. There are some studies on COVID-19 and dentistry students in the literature (14-16). Brondani and Donnelly (14) conducted a study with all dental students of the third and fourth years in the dentistry geriatric module. Quadri et al. (15) conducted a state cross-sectional study with focus on dental interns, specialists, and assistant. On the other hand, Atas and Yildirim (16) aimed to evaluate the attitudes, knowledge, and clinical training of dental students regarding the COVID-19 pandemic in their study, with a total of 355 preclinical and clinical students. In the current study, the authors aimed to examine and evaluate the knowledge levels, attitudes and anxiety sources with regard to the COVID-19 infection of dentistry faculty students who perform clinical applications.

Symptoms of COVID-19 appear from 2 to 14 days after being exposed to the virus. Common symptoms include cough, fever, difficulty breathing, and shortness of breath. Also, there may be symptoms such as body aches, fatigue, chills, loss of smell and taste, sore throat, diarrhoea, and severe vomiting. While some patients show no symptoms, others may have a combination of symptoms. Individuals with elderly or people with main chronic diseases are at high risk in terms of complications (17,18). The aerosols and droplets that occur during routine dental treatments are a possible transmission path for COVID-19 and the risk for dentists, dental students and dental assistant staff is high (19-21). This study gave us an idea of the primary awareness level of the disease of dentistry students performing clinical practice. In our study, all participants answered "true" to the following statements: "The common symptoms of COVID-19 infection include cough, fever, and shortness of breath"; "Individuals with chronic diseases are more at risk of complications than healthy individuals"; and "Health-care workers are more at risk than other workers".

In the current study, 69.3% of the students stated that antibiotics can not be used to treat the infection of COVID-19, while Atas and Yildirim (16) found a ratio of 80% in their study. The authors think this rate of 69.3% should be higher because 98.5% of the participants responded 'true' to the statement "COVID-19 infection is a viral infection".

Although the way coronaviruses are transmitted remains uncertain, the virus is believed to be initially transmitted through direct or indirect contact and respiratory aerosols. There is droplet transmission with close personal contact when a person is within one metre of someone with symptoms such as sneezing or coughing. Indirectly, the virus is transmitted by touching contaminated objects or the immediate environment used by the infected person (22,23). In the current study, 99.3% of the participants answered "true" to the following statement: "Washing hands with soap and water helps prevent disease transmission"; 88.3% of them answered "true" to the statement: "Transmission of the virus can be prevented by following the isolation rules given by the WHO". This shows us that the majority of students are aware of the individual precautions they should take. In addition, the knowledge level is important for students with limited clinical experience to protect themselves, patients and staff from infectious diseases.

In the current study, to the question "What are you most afraid of about the pandemic?", 21

(15.3%) participants answered "being infected" and 116 participants (84.7%) answered "infecting other people". In Atas and Yildirim's (16) study, the questions "Do you fear about being infected with COVID-19 as a professional health-care working at close range with the patient?" and "Do you fear about infecting any people or relatives around you regarding COVID-19 due to your closeness to the patient as a health-care worker?" were asked and the percentage of a "yes" response was 82.3% and 93%, respectively. In both studies, the participants were concerned about infecting other people in society. However, in the current study, participants were less worried about being infected with the virus. This situation is thought to be due to the differences in the time periods of when the studies were conducted. Atas and Yildirim's (16) study was conducted during the week following the first COVID-19 cases reported in Turkey. The current study was performed about five months following the first case was seen, and during this period, serious precautions were taken by the authorities to avoid spreading the epidemic throughout the country, and new information about the coronavirus was obtained from the science world.

To treat or prevent COVID-19 infection, there is currently no special antiviral drug, and patients are treated symptomatically. There are more than 200 vaccine candidates tracked worldwide. However, there is no clarity in the development of a highly immunogenic and safe COVID-19 vaccine (24). In the current study, to the question "If the COVID-19 vaccine was available, would you use it?" 102 (74.5%) participants answered "yes", 5 participants (3.6%) answered "no" and 30 participants (21.9%) answered "undecided".

In the current study, 36.5% of the participants got information on the COVID-19 from social media (Health Ministry, scientific board members, etc. and friends or health workers), 17.8% from television, 17.4% from the website of the Ministry of Health and 12.1% from scientific publications/articles. In Ikhlaq et al.'s (25) study, 384 undergraduate medical students were included and main sources of coronavirus information were television and social media - 53.1%, and 18%, respectively. Social media is easily accessible and has a wide dispersal but it may also be the source of fake information. According to these results, today it is seen that obtaining information through social media accounts is widespread and students' awareness of scientific articles should be increased. The authors think that scientific articles should be given more importance in theoretical education, and students should be supported in this issue.

With the uncertainty associated with the epidemic, most universities and dental school activities have been suspended to minimize the transmission of the virus (26,27). This means that education moved rapidly to online education and this was a relatively new practice in dental education. Despite the online distribution of most written material, direct contact between instructors, students, and patients is important both for developing clinical skills and promoting professionalism through interpersonal interactions (28). Therefore, it is normal for some students to be concerned about their clinical competence. The answers given to the following questions have a relationship with gender, and p values are 0.041, 0.019, 0.002 and 0.009, respectively: "Considering we need to get used to living with viruses, are you hesitant about the choice of the department of speciality?"; "Do you believe that the lack of face-to-face training due to COVID-19 will have negative effects when it comes to your working life?"; "Do you worry about graduating having completed clinical practices without direct patient care?"; "Do you worry about practising your job because of the coronavirus?" In these questions, we saw that females had statistically significantly higher anxiety and negativity due to COVID-19 than males. On the other hand, it has been observed that the answers given to the same questions are not related to the graduation degree. In some previous studies, it has been shown that the psychological conditions of male and female students are similarly impacted by the COVID-19 pandemic (16,29). It can be said that stressful periods more negatively affected female participants than male participants and there is an association between anxiety and this psychological condition (30). In many studies, female dental students are shown to be experience more stress than their male colleagues under normal conditions. It is thought that this is because female participants generally are stressed more intensely while male participants do not express their anxiety (31,32).

The reason why authors preferred to include dentistry students who were performing clinical

practices in the current study was that these students were in contact with patients for dental treatment and therefore thought their awareness of the risk of infection would be higher than pre-clinical students. Dentistry students experience increased patient contact throughout their clinical years, leading to them being at a higher risk of cross-infection (33). In the current study, to the question "Do you think dentists are included in the risk group for COVID-19 infection?" 97.1% of participants answered "'yes". Although they think they are in the risk group, 69.3% of them answered "no" to the following question: "Considering we need to get used to living with viruses, are you hesitant about the choice of the department of speciality?". The authors think that new outbreaks do not have a significant impact on students' choice of departments.

In the current study, 114 (83.2%) of the participants knew about COVID-19 pandemic precautions in clinical practice and 110 (80.3%) of the participants did not receive any training about COVID-19. Among health-care professionals, dental health professionals are highly exposed to infection, with serious implications for routine dental practice. Therefore, undergraduate dental students should be trained. Infection control protocols and using protective facilities are extremely important for personal safety even in asymptomatic patients.

The presented study was conducted in only two universities, which is considered to be a limitation of the study. The authors' opinion is that more accurate results can be obtained in a larger sample size with the participation of other universities.

Conclusion

Given the fact that COVID-19 is not the first pandemic that humanity has faced throughout its history and will not be the only one, it is very important to specify the attitudes, knowledge levels, and sources of anxiety of dentistry students in order to improve and reorganize dental education methods. In the present study, female students were found to be more stressed than male students in the answers given to some questions. On the other hand it has been observed that the answers given to the same questions are not related to the graduation degree. Further larger studies will give more accurate outcomes.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, Akdeniz University (decision no: KAEK-582, date: 22.07.2020), and the study was carried out in accordance with the ethical rules of the Declaration of Helsinki.

Informed Consent: Fourth- and fifth-grade students, for whom face-to-face and clinical education including direct patient care have been interrupted under the COVID-19 pandemic, were chosen for this study and the students were informed about the survey.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Y., H.T.A., E.K., Design: S.Y., H.T.A., E.K., Supervision: H.T.A., S.Y., E.K., Fundings: H.T.A., S.Y., E.K., Materials: H.T.A., S.Y., Data Collection or Processing: H.T.A., S.Y., Analysis or Interpretation: H.T.A., Literature Search: H.T.A., S.Y., E.K., Critical Review: H.T.A., S.Y., E.K., Writing: H.T.A., S.Y., E.K.

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Original Article / Özgün Araştırma

Evaluation and Comparison of Root Resorption Resulting from Traditional and Bone-borne Rapid Maxillary Expansion Appliances Using Cone-beam Computed Tomography

Konik Işınlı Bilgisayarlı Tomografi Kullanılarak Geleneksel ve Kemik Destekli Hızlı Üst Çene Genişletme Yöntemlerinin Kök Rezorpsiyonuna Etkisinin Değerlendirilmesi ve Karşılaştırılması

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Abstract

Objective: This study aimed to evaluate the resorptions of the roots of the maxillary posterior teeth after traditional rapid maxillary expansion (TRME) therapy and bone-borne rapid maxillary expansion (BBRME) appliances and to compare the findings obtained using the two appliances.

Materials and Methods: The study enrolled 40 patients treated at the orthodontics clinic. These patients were divided into the TRME group (13.4±1.2 years old, n=20) and BBRME group (13.2±1.3 years old, n=20) according to the appliance used. Cone-beam computed tomography images taken before the treatment (T0) and after a 3-month retention period (T1) was transferred to an image-processing software. Volumetric measurements of the teeth were made after the segmentation procedure, and volumetric changes before and after treatments were analysed statistically. Paired-sample t-test was used for the intra-group comparison, and independent-sample t-test was used for the inter-group comparison.

Results: In both groups, the amount of resorption in all teeth that occurred between T0 and T1, was statistically significant ($p<0.001$). In the TRME group, the highest resorption was measured in the 1st molars (79.65 mm^3), and the lowest resorption was measured in the 2nd premolars (33.38 mm^3). In the BBRME group, the highest resorption was measured in the 1st molars (46.74 mm^3), and the lowest resorption was measured in the 1st premolars (21.61 mm^3). In the comparison of root resorptions that occurred between T0 and T1 in the two groups, analysis results showed that the BBRME group demonstrated lower root resorption ($p<0.05$).

Conclusion: The results suggest that BBRME causes less root resorption than TRME.

Öz

Amaç: Bu çalışmanın amacı, geleneksel hızlı üst çene genişletme (GHÜÇG) ve kemik destekli hızlı üst çene genişletme (KDHÜÇG) yöntemlerinin arka üst diş köklerinin rezorpsiyonuna etkisini değerlendirmek ve iki cihaz kullanılarak elde edilen bulguları karşılaştırmaktır.
Gereç ve Yöntemler: Çalışma ortodonti kliniğinde tedavi gören 40 hasta ile yapılmıştır. Çalışma iki grup halinde tasarlanmıştır. Birinci grup GHÜÇG ile tedavi edilen 20 hastadan (13,4±1,2 yaş), ikinci grup ise KDHÜÇG cihazları ile tedavi edilen 20 hastadan (13,2±1,3 yaş) oluştu. Hastalardan tedavi öncesi (T0) ve 3 aylık tutma (T1) sonrası alınan konik ışınlı bilgisayarlı tomografi kayıtları programa aktarıldı. Segmentasyon işleminden sonra dişlerin hacimsel ölçümleri yapıldı ve tedavi öncesi ve sonrası hacimsel değişimler istatistiksel olarak analiz edildi. Grup içi karşılaştırmada bağımlı örnek t-testi, gruplar arası karşılaştırmada ise bağımsız-örneklem t-testi kullanıldı.
Bulgular: Her iki grupta da T0-T1 arasında meydana gelen tüm dişlerde rezorpsiyon miktarı istatistiksel olarak anlamlı bulundu ($p<0,001$). GHÜÇG grubunda en yüksek rezorpsiyon 1. büyük azılarda (79,65 mm^3), son olarak en düşük rezorpsiyon 2. küçük azılarda (33,38 mm^3) ölçüldü. KDHÜÇG grubunda en yüksek rezorpsiyon 1. büyük azılarda (46,74 mm^3), son olarak en düşük rezorpsiyon 1. küçük azılarda (21,61 mm^3) ölçüldü. T0 ile T1 arasında meydana gelen kök rezorpsiyonunun iki grupta karşılaştırılmasında, statik olarak sonuçlar KDHÜÇG grubunun daha düşük kök rezorpsiyonu meydana getirdiğini göstermiştir ($p<0.05$).
Sonuç: Kemik destekli hızlı üst çene genişletmenin, geleneksel hızlı üst çene genişletmeye göre daha az kök rezorpsiyonuna neden olduğu kanıtlanmıştır.

Introduction

Rapid maxillary expansion (RME), used frequently in cases of maxillary transversal constriction, was first introduced by Emerson C. Angell in 1860 (1). Interest in RME increased in the late 1940s when Graber claimed that RME was necessary for the treatment of patients with cleft lip and palate (2). Later, this method gained popularity following Haas' studies (3). Numerous different RME appliances have been designed up till now. The studies and resulting advancements in RME tecniques have enabled clinician to adopt various treatment strategies by choosing the most appropriate appliance type for the case (4-7).

Forces transmitted by RME exert, orthopedic effects occur on maxilla that cause maxillary expansion by sutural opening (8). Severe forces required for this sutural opening may cause side effects on the covered tooth such as resorption (9,10), fenestration (11) and dental tipping (2,12). Bone-borne rapid maxillary expansion (BBRME) appliances were designed with the developments in the skeletal anchorage in order to prevent or at least to decrease these disadvantages. Force is directly transmitted to the maxilla with the help of anchorage units in BBRME (13). Different types were applied according to the miniscrew number and location (6,7,14). Hybrid expander, designed by Akin et al. (14), is supported by acrylic pads and two miniscrews placed on the palatal bone between the 2nd premolar and the 1st molar.

Two dimensional radiographic methods are inadequate for the detailed measurements of root resorption owing to magnification, distortion and superimpositions (15-17). Three dimensional (3D) screening methods enables more reliable measurements by eliminating these disadvantages (15). Among 3D techniques, micro computed tomography (CT) and SEM are used *in vitro*, therefore the studied teeth should be extracted teeth (18). Cone-beam CT (CBCT) is preferred for the *in vivo* studies (7,10,17).

The aim of this study is to measure root resorptions of 1st molar, 1st premolar and 2nd premolar teeth after the therapy with traditional rapid maxillary expansion (TRME) and BBRME appliances, and to compare these findings between two appliances. The null hypothesis of our study is, between TRME and BBRME there would not be any difference in the amount of root resorption after the retention period.

Materials and Methods

Patient records of this retrospective study were collected after obtaining the Selçuk University, Faculty of Dentistry Ethics Committee Approval in Non-Invasive Clinical Trials (protocol no: 2015/01, date: 08.10.2015). Forty patients (20 girls, 20 boys) who had been treated by RME in Selçuk University, Department of Orthodontics, were included in the study.

The sample size for the study was determined by using G*Power analyses (Ver.3.0.10 Franz Faul Universitat, Kiel, Germany). At 0.45 effect size and 0.05 significance level in two group and repeated measurements 40 patients had given 89.4% power. They were divided into two groups, each consisting of 20 individuals. The inclusion criteria are in Table 1.

The first group consisted of 8 girls and 12 boys with a mean age, 13.4±0.1 years; range, 12.2-14.8 years. All patients and their parents were informed about the research and signed informed consent forms. These patients were treated with modified acrylic cap splint (Figure 1) RME appliance and had CBCT records taken at the beginning of the treatment and after 3 months retention period.

The second group consisted of 12 girls and 8 boys with a mean age, 13.2±0.1 years; range, 11.8-14.5 years. These patients were treated with the Hybrid expander (Figure 2) for BBRME appliance and had CBCT records taken at the beginning of the treatment and after a 3 month retention period.

All tomographic records were taken by the same machine (Kodak, CS 9300, Carestream Health Inc, Rochester, NY) and at the following settings: 8.0 mA and 70 kV for 6.15 seconds, 0.18 mm axial slice thickness. CBCT records of the patients were configurated as 3D after being transferred to Mimics Innovation Suite (Version 10.01 Materialise, Leuve, Belgium). First, the density settings were applied for the transferred images. The most appropriate density ranges for the segmentation of the teeth were decided for each patient. CBCT records, taken in the beginning of the treatment and 3 months after the retention period, of each patient were segmented in the same density setting. On these 3D images, permanent first molars and first and second premolars were segmented.

After the segmentation of the 1st premolar, 2nd premolar and the 1st molar teeth, they were isolated by splitting the surrounding structures (Figure 3). The volumetric measurements of the isolated teeth were made and changes occuring at the beginning and after the retention were recorded (Figure 4). Percentage changes of the teeth volumes were also recorded by calculating the ratio as T0-T1 (change in volume) /T0 (initial volume).

Table 1. Inclusion and exclusion criteria
The following are criteria for the inclusion of patients
Who had bilateral contsriction on the maxillary basal bone.
Who achieved 7-9 mm sutural expansion after the treatment.
Who did not have any orthodontic treatment before the RME therapy.
Who used the RME appliance properly.
Who were in the permanent dentition.
Who had CBCT record preexpansion and post retention.
Who are 12-15 years old.
The following are criteria for the exclusion of patients
Who had apical lesions, cyst and anomalies on the covered teeth.
Whose teeth's root closings were not completed.
Whose teeth were missing.
Who had coronal restorations on the covered teeth.
Who did not have sufficient CBCT records.
CBCT: Cone-beam computed tomography, RME: Rapid maxillary expansion

Figure 1. Modified acrylic cap splint rapid maxillary expansion appliance

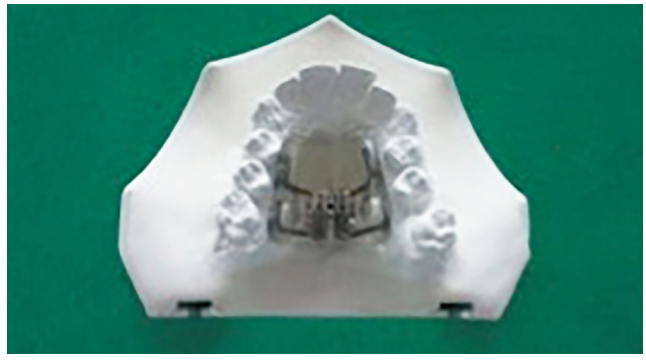

Figure 2. Hybrid expander rapid maxillary expansion appliance

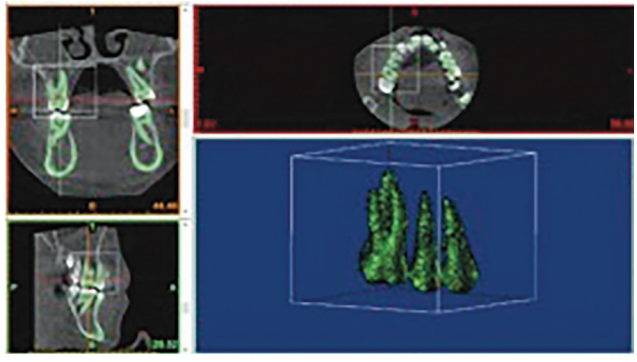

Figure 3. After the segmentation of 1st premolar, 2nd premolar ve 1st molar teeth, teeth were isolated by splitting the surrounding structures

Statistical Analysis

Normality of the collected data was tested by Shapiro-Wilk normality test, and it was found that the results of the two groups were normally distributed. For the intragroup evaluation, Paired Sample t-test was used for the comparison of volumetric measurements before expansion (T0) and after retention (T1) in both groups.

For the intergroup evaluation, Student's t-test was used for comparing volumetric measurements between two groups, considering numerical and percent volumetric changes. Test results are presented as mean and standard deviation in the tables. P<0.05 value was used for the statistical significance.

To examine the error associated with digitizing and measurements, 15 images were selected randomly and all procedures (landmark identification, tracing, measuring) were repeated three weeks after the first examination, by the same orthodontist (O.O.) without knowledge of the first measurements. Intra-class correlation coefficients, performed to assess the reliability of the measurements, showed that the values were over 0.951, confirming the reliability of the measurements. The results of the paired t-test to assess the systemic error showed that all measurements were free of systemic error (p>0.05).

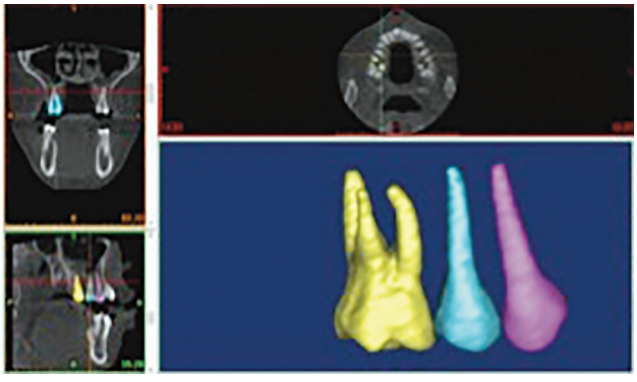

Figure 4. The volumetric measurements of the isolated teeth were made and changes occurred in the beginning and after the retention were recorded

Results

Intragroup Comparison

The amount of expansion was measured as 7.96 mm in the first group and as 7.67 mm in the second group. The mean age was 13.4 ±1.2 years in the first group and 13.2±1.3 years in the second group. There was no significant difference between the groups in the amount of expansions and mean ages (p>0.05).

In the first group, the mean volumetric measurement was 584,021±49,009 mm^3 before the expansion and 546,249±48,475 mm^3 after the retention for the 1st premolar. Mean volumetric measurement was 557,854±34,531 mm^3 before the expansion and 524,472 ± 34,777 mm^3 after the retention for the 2nd premolar. Mean volumetric measurement was 1226,584±62,003 mm^3 before the expansion and 1146,932±67,541 mm^3 after the retention for the 1st molar. All these decreases were statistically significant (p<0.05) (Table 2).

In the second group, the mean volumetric measurement was 567,85±57,158 mm^3 before the expansion and 545,568±57,187 mm^3 after the retention for the 1st premolar. Mean volumetric measurement was 540,726±52,639 mm^3 before the expansion and 516,117±58,719 mm^3 after the retention for the 2nd premolar. Mean volumetric measurement was 1218,423±69,984 mm^3 before the expansion and 1172,285±63,144 mm^3 after the

Table 2. Results of traditional rapid maxillar expansion and bone-borne rapid maxillar expansion at T0 and T1

Group	Tooth	T0 (mm^3)		T1 (mm^3)		p
		Mean	SD	Mean	SD	
TRME appliance	1st Premolar	584.021	49,009	546,249	48,475	<0.001***
	2nd Premolar	557,854	34,531	524,472	34,777	<0.001***
	1st Molar	1,226,584	62,003	1,146,932	67,541	<0.001***
BBRME appliance	1st Premolar	567,185	57,158	545,568	57,187	<0.001***
	2nd Premolar	540,726	52,639	516,117	58,719	<0.001***
	1st Molar	1,218,423	69,984	1,172,285	63,144	<0.001***

TRME: Traditional rapid maxillary expansion, BBRME: Bone-borne rapid maxillary expansion, T0: In the beginning, T1: After 3 months, SD: Standard deviation, p<0.05 value was used for the statistical significance, *p<0.05, **p<0.01, ***p<0.001

retention for the 1st molar. All these decreases were statistically significant (p<0.05) (Table 2).

Intergroup Comparison

The null hypothesis of our study was rejected. The mean amount of root resorption in the 1st premolar was measured as 37,772±10,644 mm^3 in the first group, and as 21,617±11,251 mm^3 in the second group, which was statistically significant less than first group (p<0.05) (Table 3).

The mean amount of root resorption in the 2nd premolar was measured as 33,382±11,474 mm^3 in the first group, and as 24,609±15,398 mm^3 in the second group, which was statistically significant less than first group (p<0.05) (Table 3).

The mean amount of root resorption in the 1st molar was measured as 79,651±13,278 mm^3 in the first group, and as 46,148±20,964 mm^3 in the second group, which was statistically significant less than first group (p<0.05) (Table 3).

The percental volumetric decreased for the 1st premolar was 6.48% in the first group and 3.82% in the second group, which was statistically significant less than first group (p<0.05) (Table 4).

The percental volumetric decreased for-the 2nd premolar was 5.98% in the first group and 4.67% in the second group, which was not statistically significant less than first group (p>0.05) (Table 4).

The percental volumetric decreased for-the 1st molar was 6.53% in the first group and 3.76% in the second group, which was statistically significant and less than first group (p<0.05) (Table 4).

Discussion

When the orthodontic literature was reviewed, not to much study based on 3D comparison of root resorptions after using TRME and BBRME appliances was found.

According to numerous studies, the most appropriate age for the performing RME is 8-15 years (2). The existence of open root apex may negatively influence the measurements of root resorption and may compromise the reliability of results (18). In accordance with this information, patients between 12-15 years of age were included in this study.

Bonded appliances, covering all the surfaces of posterior teeth, were designed in order to provide better vertical control. Acrylic parts extending to the occlusal surfaces of the teeth also act as bite blocks. Therefore, forces provided by the miniscrew can be transmitted directly to the suture without any obstacles (19,20). Some studies claim that less root resorption occurs with usage of these appliances (21).

Table 3. Comparison of the results of traditional rapid maxillar expansion and bone-borne rapid maxillar expansion at T0 and T1

Tooth	TRME (n=20)		BBRME (n=20)		p
	Mean	SD	Mean	SD	
1st Premolar	37,772	10,644	21,617	11,251	<0.001***
2nd Premolar	33,382	11,474	24,609	15,398	0.048*
1st Molar	79,651	13,278	46,148	20,964	<0.001***

TRME: Traditional rapid maxillary expansion, BBRME: Bone-borne rapid maxillary expansion, T0: In the beginning, T1: After 3 months, SD: Standard deviation, p<0.05 value was used for the statistical significance, *p<0.05, **p<0.01, ***p<0.001

Table 4. Comparison of the results of traditional rapid maxillary expansion and bone-borne rapid maxillary expansion at T0 and T1

Tooth	TRME (n=20)		BBRME (n=20)		p
	mm^3	%	mm^3	%	
1st Premolar	37,772	6.68%	21,617	3.82%	<0.001***
2nd Premolar	33,382	5.98%	24,609	4.67%	0.117
1st Molar	79,651	6.53%	46,148	3.76%	<0.001***

TRME: Traditional rapid maxillary expansion, BBRME: Bone-borne rapid maxillary expansion, T0: In the beginning, T1: After 3 months, SD: Standard deviation, p<0.05 value was used for the statistical significance, *p<0.05, **p<0.01, ***p<0.001

Considering this, the first group was formed using the records of the patients who were treated by full coverage traditional RME.

BBRME appliances are placed on the palatal vault. Forces transmitted to the maxilla pass nearer to the center of resistance of the maxilla in BBRME than in TRME, that's why more parallel expansion may be achieved by BBRME appliances (7,22). Another advantages of BBRME are usage in hipodontia cases, usage for patients having periodontological problems, being more hygienic. However, longer and troublesome laboratory procedures and difficulty in appliance are the disadvantages of BBRME (6,23).

Hybrid expander constists of two miniscrews placed on the palatal bone and the acrylic part covering these screws. It was showed that 2 miniscrews could counter the forces provided by the RME appliance with this method (14). We prefer Hybrid expander in our clinic due to some advantages such as less cost, easy in practice, reduction of side effects caused by the screw, patient acceptance, no requirement of another appliance for the retention. In addition, Akin et al. (14) used acrylic raised lower essix plaque to diminish occlusal contacts and resistance. Patients who also used acrylic raised lower essix plaque during their expansion was chosen for our study.

CBCT was developed to display small areas like the maxilla in *in vivo* studies. Low-dose radiation and lower costs are the prominent advantages of the method (7,10,17). Moreover, accurate and precise findings were attained from the maxillofacial area in some studies (24). Therefore, CBCT radiographs of the patients taken before and after the treatment were used for our study.

Bishara and Staley (2) stated in their studies that the expansion appliance should be kept in the mouth for 3-6 months for the retention and that tension occurred on the soft tissues surrounding the maxilla after RME which was a substantial level considering relapse.

The hyrax appliance was used in 18 patients in Langford and Sims (25) study. After the expansion procedure, patients' retention procedure lasted for 14-53 weeks. Then, 1st premolars were extracted and root resorptions were observed under the electron microscope. In the study, active root resorption was observed in the first 3 months. Measurements were made on CBCT records taken 3 months after the expansion in both groups to be able to observe resorption process better.

In our study, statistically significant root resorption occurred for all the teeth in the first group. The greatest resorption occurred in the 1st molar, followed by the 1st premolar, and the lowest resorption occurred in the 2nd premolar. These findings were similar to those of Dindaroğlu and Doğan (10) studies, in which root resorption was observed after bone borne RME and ranking of root resorptions of the teeth were the same as that obtained study.

Although ranking of root resorptions of the teeth was the same, as that obtained in the study of Baysal et al. (17), less root resorption was observed. However, teeth were cut from the furcation parts in that study while measuring the root resorption. So, root resorptions in the cervical parts could not be measured. The difference in the root resorption amount between the two studies may be due to this reason. The other reason of this difference may be that since T2 records were taken just after the expansion, the resorption process could not be completed as Baysal et al. (17) also reported.

In the second group, statistically significant root resorption occurred in all the teeth. Odenrick et al. (26) stated that root resorption was observed also on the uncovered teeth. The results gained from the uncovered teeth in our study were similar to Odenrick's findings.

Results obtained after three months of retention in Barber and Sims (9) study considering root resorption were compatible with the results of the first group in our study. However, authors claimed that the uncovered teeth were exposed to lateral movement and relaps thereafter, and that resorption occurred as a result. These findings contradicted with the results of our second group.

Langford and Sims (25) reported that severe relapse forces arised in the first 3 months after RME causing root resorption. In the second group of our study, since the teeth were uncovered, the forces provided by soft tissue tensions after the expansion were directly transmitted to teeth. The reason of observing root resorption in the second group although there was no direct force transmission to the teeth may be results of the relapse forces.

Statistically more significant resorption occurred in the first group than in the second group. In Lin et al.

(7) study, dental and skeletal effects of tooth borne and bone borne RME appliances on the maxilla were compared. There was statictically more dental tipping for all teeth in the tooth borne group. There are many studies showing that BBRME appliances cause less dental tipping (14,23). That might be the reason of less resorption observed in the second group compared to the first group in our study.

This result supports the hypothesis defended by the authors researching bone borne RME that less root resorption occurs after bone borne RME (6,13,14,27).

Conclusion

Statistically significant root resorption occurred in both TRME and BBRME groups. The greatest resorption occurred in the 1st molar, followed by the 1st premolar, and the lowest resorption occurred in the 2nd premolar in first group.

The greatest resorption occurred in the 1st molar, followed by the 2nd premolar, and the lowest resorption occurred in the 1st premolar in second group.

Percental root resorption change in the 1st molar and for the 1st premolar in the first group were statistically more significant than that in the second group; however no statistically difference was observed for the 2nd premolar.

When the root resorption was compared between the groups, statistically lower significant root resorption was observed for all teeth in the BBRME group than in-the TRME group.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the Selçuk University Faculty of (protocol no: 2015/01, date: 08.10.2015).

Informed Consent: All patients and their parents were informed about the research and signed informed consent forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.A., Design: M.A., Supervision: M.A., O.Ö., Fundings: M.A., O.Ö., Materials: O.Ö., Data Collection or Processing: O.Ö., Analysis or Interpretation: M.A., Literature Search: O.Ö., Critical Review: M.A., Writing: M.A., O.Ö.

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Original Article / Özgün Araştırma

Evaluation of the Clinical Success of Implant - Supported Restorations- A Retrospective Study with at Least Two Years of Follow-up

İmplant Destekli Restorasyonların Klinik Başarısının Değerlendirilmesi: En Az İki Yıllık Takip ile Restrospektif Çalışma

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Abstract

Objective: This retrospective clinical study aimed to investigate the long-term clinical success of dental implants restored with splinted or non-splinted posterior prostheses with different retention systems.

Materials and Methods: Fifty patients who had undergone dental implant surgery and prosthesis treatment and had a follow-up period of at least 2 years were included in this study. Marginal bone loss was measured from the surrounding bone levels on the mesial and distal surfaces of the implants using a millimetre ruler on panoramic radiographs. The plaque index (PI), gingival index (GI) and bleeding on probing (BOP) were also measured. The Mann-Whitney U test and ANOVA test were used for statistical analysis.

Results: The mean values of mesial and distal bone loss were 0.72±0.81 and 0.62±0.58, respectively. The correlation coefficient between mesial and distal bone loss was 0.431; thus, a significant difference was found ($p<0.05$). A significant relationship was found between the GI ($p=0.004$) and PI ($p=0.000$) of dental implants with different retention types. No significant relationship was observed between BOP and retention type ($p>0.05$).

Conclusion: Clinically, given the long-term maintenance of soft and hard tissue health, successful results can be achieved with a two-member fixed prosthetic rehabilitation plan on two implants.

Öz

Amaç: Bu retrospektif klinik çalışma, posterior bölgedeki farklı retansiyon sistemlerine sahip splintli veya tek başına planlanan protetik tedavinin dental implantların uzun vadeli klinik başarısına etkisini değerlendirmektedir.

Gereç ve Yöntemler: Çalışmaya, dental implant cerrahisi ve sonrasında protetik tedavi uygulanan ve en az iki yıllık takip süresi olan 50 hasta dahil edildi. Marjinal kemik kaybı, panoramik radyografiler üzerinde milimetrik bir cetvel kullanılarak implantların mezial ve distal yüzeylerini çevreleyen kemik seviyeleri göz önüne

alınarak değerlendirildi. Ayrıca plak indeksi (PI), diş eti indeksi (GI) ve sondalama sırasında kanama (BOP) değerleri kaydedildi. İstatistiksel analiz için Mann-Whitney U testi ve ANOVA testi kullanıldı.
Bulgular: Mezial ve distal kemik kaybı ortalamaları sırasıyla 0,72±0,81 ve 0,62±0,58 bulundu. Mezial ve distal kemik kaybı arasındaki korelasyon katsayısı 0,431 olduğu için istatistiksel olarak anlamlı bir fark olduğu sonucuna varıldı ($p<0,05$) Farklı retansiyon tiplerine sahip diş implantlarının GI ($p=0,004$) ve PI ($p=0,000$) değerleri arasında istatistiksel olarak anlamlı bir ilişki bulundu, fakat BOP ile retansiyon tipi arasında istatistiksel olarak anlamlı bir ilişki olmadığı görüldü ($p>0,05$).
Sonuç: Klinik olarak, yumuşak ve sert doku sağlığının uzun süreli idamesi göz önüne alındığında iki implant üzerine planlanan iki üyeli sabit protetik rehabilitasyon ile başarılı sonuçların elde edilebileceği düşünülmektedir.

Introduction

Dental implants are the preferred treatment method for the rehabilitation of missing teeth because of their predictable results and high survival and success rates. To achieve predictable long-term results and obtain a favorable prognosis, the number and position of the implants, intermaxillary distance, and quality and quantity of alveolar bone should be comprehensively evaluated before implant surgery (1). Dental implants have several advantages, including a long-term success rate of up to 97%, reduced risk of caries and endodontic problems of corresponding teeth, and preservation of bone in the edentulous site, compared with conventional prostheses (2).

Successful implant treatment results depend on the continuity of the volume and quality of the bone surrounding the implant. Although the diseases that occur in the tissues around dental implants and natural teeth show many common clinical features, the significant structural differences between them are clearly obvious, especially in relation to the surrounding tissues and biological attachment (3). The most important difference is the absence of cement and periodontal ligament around the dental implant, which can limit bacterial penetration. There are also differences in the connection between the tooth and the dental implant with alveolar bone. While there is a direct structural and functional connection between the dental implant and alveolar bone defined as osseointegration, natural teeth also attach to the alveolar bone through Sharpey fibers and the periodontal ligament (4).

Implant-supported superstructures can be fixed using two methods: Cement-retained and screw-retained. Both methods can be performed for single, multiple, and full-arch fixed dental prostheses, and both have pros and cons. The screw-retained type has predictable retrievability and easier maintenance, but the screw hole can cause esthetic and occlusal problems. As for the cement-retained type, although it is easy to achieve passivity of fit and provide occlusion control, leaving excess cement is the principal reason for peri-implant tissue disease. The choice of retention type can affect the survival rate of dental implant treatment and influence the development of complications (1). Therefore, it is the clinician's responsibility rather than scientific research to decide on the most suitable retention system. Both systems are subject to technical and biologic complications (5-7). Biologic complications include peri-implant disease, crestal bone loss, and implant failure. Adequate clinical and radiographic examination methods are required to detect these complications (3,7). Dental radiographs are commonly used before treatment (in the diagnosis and planning of implant surgery) and after treatment (in assessing the adaptation of prosthetic restorations and detecting bone loss).

Peri-implant diseases are classified as peri-implant mucositis and peri-implantitis. Peri-implant mucositis is defined as peri-implant soft tissue inflammation characterized by redness, swelling, and short-term bleeding without bone loss (8). Peri-implantitis is described as a plaque-related pathological condition characterized by inflammation in the surrounding mucosa of the dental implant and progressive bone loss around the implant. Peri-implantitis shows signs of clinical inflammation, such as bleeding or exudation, increased probe depth, and increased resorption of peri-implant bone compared with previous radiographs (9).

Various studies have proved that the retention type of implant prosthesis has an important effect on the incidence of peri-implantitis (10-12). Physicians should develop a plan to predict potential peri-implant diseases, evaluate risk factors, and consider alternative treatment methods. They should also have comprehensive knowledge of overall treatment

options. In the current study, the long-term success and periodontal health of dental implants restored with splinted or non-splinted posterior prostheses and different retention systems with at least two years of follow-up were investigated.

Materials and Methods

This retrospective clinical study was carried out at Uşak University with ethical committee approval number 41-11-20 (date: 22.07.2020). The protocol of the study was conducted according to the principles described in the Declaration of Helsinki, including all changes and revisions. A total of 50 patients, including 28 males and 22 females, who had previously undergone dental implant surgery and prosthesis treatment at Uşak University Faculty of Dentistry from 2016 to 2020 and attended regular follow-up appointments for at least two years were included. All patients were informed and included in the study after obtaining their consent.

The patients were systemically healthy but partially edentulous in the posterior region. Patients were excluded from the study in case of implant treatment failure, parafunctional habits, signs of wear on the occlusal surface of the teeth, or failure to attend follow-up appointments. Radiographs were taken immediately after prosthetic treatment and at annual controls. Marginal bone loss was measured from the surrounding bone levels on the mesial and distal surfaces of the implants using a millimeter ruler in the instruments section of the radiographic imaging application (PCH-2500 Digital X-Ray Imaging System, PaX-i, VATECH, Hwaseong-si, Korea). To provide calibration, the margin of error was calculated by comparing the implant length in the image with the accurate implant size. The calibration process allowed for more definitive results and standardization of radiographic measurements. The difference between measurements in after-loading and control radiographs was recorded while considering bone loss. When there was more than one image in the region where the implant was in contact with the crest, the most apical contact point was evaluated.

In addition to bone loss measurements from each patient's control radiographs, six points of plaque index (PI) (13), gingival index (GI) (14), and bleeding on probing (BOP) were measured from the surrounding region of the implants to evaluate clinical success. The bleeding values in pocket depth and probing were measured and recorded by taking the average of the obtained data. By comparing the number of members and the type of retention, the relationship between bone loss and periodontal health was investigated.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS version 25.0 (IBM Corp., NY, USA) program. The normality assumption was checked using the Shapiro-Wilk test as the first step of data analysis. The Mann-Whitney U test was applied to examine the difference between the two groups without a normal distribution and independently. The ANOVA test was conducted to examine the difference between the means of variables with more than two independent groups with a normal distribution. The Kruskal-Wallis test was used to examine the difference in the averages of variables with more than two independent groups that did not have a normal distribution. In the analysis of categorical variables, Fisher's Exact test was used in cases in which the assumption of sample size was not provided. The relationship between continuous data without a normal distribution was tested using Spearman's correlation. The G* Power 3.1.9.2 program was used to calculate the adequacy of the sample size at a 95% confidence level. The level of statistical significance was set to $p<0.05$.

Results

The mean follow-up duration of the patients was 3.4 years. The distribution of the participants according to their demographic characteristics is shown in Table 1. According to gender, 44.0% of the patients were female and 56.0% were male (Table 1). The distribution

Table 1. Distribution of people participating in the research according to demographic features

Demographic features		n	%
Gender	Female	22	44.0
	Male	28	56.0
Age	31 year and younger	3	6.0
	32-43	14	28.0
	44-55	13	26.0
	56 year and older	20	40.0

of dental implants according to retention type and number of units is shown in Table 2. The averages of mesial (0.72±0.81) and distal (0.62±0.58) bone loss are shown in Table 3. The correlation coefficient between mesial and distal bone loss was found to be 0.431, with p=0.000 lower than the alpha value (0.05), and thus a statistically significant difference was determined (Table 4).

A statistically significant difference was found between the mesial and distal bone loss of single and splinted two-unit and three-unit prosthetic superstructures (p=0.043). However, there was no

Table 2. Distribution of dental implants examined by cementation and number of members

Total dental implants		n	%
Cementation and number of units	Single cement	19	16.0
	Single screw-retained	12	10.1
	2-Unit cement	24	20.2
	2-Unit screw-retained	16	13.4
	3-Unit cement	26	21.9
	3-Unit screw-retained	22	18.4
Cementation	Cement	69	58.0
	Screw-retained	50	42.0
Number of units	Single	31	26.1
	2-Units	40	33.6
	3-Units	48	40.3

Table 3. Mesial and distal bone loss averages and standard deviations

Total dental implants	n	Minimum	Maximum	x̄	SD
Mesial bone loss	119	0.00	4.10	0.7271	0.81083
Distal bone loss	119	0.00	2.42	0.6246	0.58113

SD: Standard deviation

Table 4. The relationship between mesial bone loss and distal bone loss

	Distal bone loss	
	Rho	p
Mesial bone loss	0.431	0.000*

*p<0.05

Table 5. Comparison of mesial and distal bone loss averages according to cementation and number of units

	Mesial bone loss					Distal bone loss				
	Cementation		Number of units			Cementation		Number of units		
	Cement	Screw-retained	Single	2-Unit	3-Unit	Cement	Screw-retained	Single	2-Unit	3-Unit
n	69	50	31	40	48	69	50	31	32	44
x̄	0.7350	0.7163	0.7519	0.5751	0.8378	0.6712	0.5602	0.6920	0.4268	0.7458
SD	0.81793	0.80909	0.98836	0.56414	0.85466	0.57385	0.59074	0.55577	0.41628	0.67499
Mean rank	59.93	60.09	56.24	56.91	65.00	63.56	55.09	65.71	48.85	65.60
*p	0.981		0.428			0.186		0.043*		

*p<0.05, SD: Standard deviation

statistically significant difference between retention type and marginal bone level (p>0.05) (Table 5).

A statistically significant relationship was found between the GI (p=0.004) and PI (p=0.000) of dental implants with different retention types (p<0.05) (Table 6). However, there was no statistically significant relationship between BOP and retention type (p>0.05). The relationship between different prosthetic superstructures was not statistically significant in terms of GI, PI, and BOP (p>0.05) (Table 7).

Discussion

The survival rate of dental implants is a key factor in achieving long-term clinical success in dental implant treatment aimed at esthetic and functional improvement. Oral diagnosis and

Table 6. Comparison of plaque index, gingival index and bleeding on probing index with different cementation, cross chart and Pearson chi-square test results

		Cementation					
		Cemented		Screw-retained			
		n	%	n	%	Pearson chi-square	p*
GI score	0	19	39.6	29	60.4	11.187	0.004*
	1	40	70.2	17	29.8		
	2	10	71.4	4	28.6		
	3	0	0.0	0	0.0		
PI score	0	19	36.5	33	63.5	17.447	0.000*
	1	39	75.0	13	25.0		
	2	11	73.3	4	26.7		
	3	0	0.0	0	0.0		
BOP	+	58	55.8	46	44.2	1.660	0.198
	-	11	73.3	4	26.7		

*p<0.05, PI: Plaque index, GI: Gingival index, BOP: Bleeding on probing

Table 7. Comparison of plaque index, gingival index and bleeding on probing index with different number of units cross chart and Fisher's Exact test results

		Unit number							
		1		2		3			
		n	%	n	%	n	%	Fisher's Exact test	p
GI	0	11	22.9	20	41.7	17	35.4	3.893	0.421
	1	15	26.3	18	31.6	24	42.1		
	2	5	35.7	2	14	7	50.0		
	3	0	0.0	0	0.0	0	0.0		
PI	0	11	21.2	22	42.3	19	36.5	5.129	0.274
	1	14	26.9	16	30.8	22	42.3		
	2	6	40.0	2	13.3	7	46.7		
	3	0	0.0	0	0.0	0	0.0		
BOP	+	25	24.0	38	36.5	41	39.4	3.553	0.169
	-	6	40.0	2	13.3	7	46.7		

*p<0.05, PI: Plaque index, GI: Gingival index, BOP: Bleeding on probing

planning are essential to accomplish desirable dental implant outcomes. A comprehensive preoperative assessment consists of medical history and intraoral and radiographic evaluation. In the examination before implant surgery, width, height, and quality of bone should be evaluated, and the presence of pathology should be investigated. In dental implant treatment, rehabilitation is considered successful if the osseointegration can function properly and physiologically (15,16).

In the present study, the long-term success and periodontal health of single and splinted two-unit and three-unit prosthetic superstructures with different retention systems were investigated.

In the first year, surrounding bone loss of a dental implant after loading of up to 1.0 mm is expected in the healing process, but radiographic evidence of any additional bone loss suggests peri-implant disease (17). However, during the first year of dental implant rehabilitation, greater bone loss may occur due to the irregular distribution of stress or excessive occlusal force (18,19). The opinion that has been accepted in previous decades is that bone loss around the dental implant greater than 2.0 mm after the first year of prosthetic loading is a peri-implantitis finding (20).

When the parameters affecting bone loss are examined, implant-abutment connection, retention type, prosthetic treatment plan, and patient habits should be considered (21-24). According to the results of the current study, there is a significant relationship between the prosthetic treatment plan and marginal bone loss (p=0.043). These results are similar to those of a previous study that compared narrow and wide implants and also observed greater bone loss in the distal area with wide implants (22). In terms of prosthetic superstructures, the single-unit prosthesis group had more distal bone loss than the two-unit splinted on two implant prostheses. A significant difference was found in a previous study, but contrary to the current study, the marginal loss was higher in the splinted group than in the single-unit prosthesis (25). Conversely, other researchers found no significant difference (22,26,27). These conflicting results may originate from the implant location in the jaw or prosthetic features. The current study concluded that there was a statistically significant difference between the two-unit and three-unit splinted on two implant prostheses, and the presence of pontic between the two implants increased bone loss in the distal implant. Higher bone loss between the splinted groups may be due to insufficient oral care, especially under pontic, and progressive occlusal force. The effect of meticulous cleaning and hygiene around molars, which are more difficult to reach than anterior teeth, on long-term bone loss should not be ignored (25,26)

Although not statistically significant, it is worth mentioning that marginal bone loss was affected by retention type and that there were higher marginal bone loss values in the cemented type. Repeated abutment replacement in the cemented type during the whole prosthetic treatment is considered to break down the integrity of the surrounding periodontal tissue and to rupture the connective tissue, facilitating the penetration of bacteria compared with the screw-retained type. These outcomes are consistent with previous studies (28-31).

Bleeding, probing depth (PD), and bone loss values are important for the long-term success of implant treatment (32). There are many studies on the relationship between clinical periodontal status and marginal bone loss (20,33,34). Malmstrom et al. (34) found no significant relationship between bone loss and the GI, PI, and PD measurements of dental implants of different lengths in the maxilla and mandible. On the contrary, according to the present study, there was a significant difference between GI (p=0.004) and PI (p=0.00) in both retention groups. The highest values were recorded around the cemented type compared with the screw-retained type. However, the absence of a significant difference in PD indicates that there was no significant difference in terms of bone loss according to retention type. Biological complications are more common in cemented-type prostheses due to the large quantity of cement remnants present in the peri-implant sulcus after cementation (10-12). Similar to the present study, Weber et al. (35) mentioned that during follow-up, cemented-type prostheses always had a greater degree of gingival bleeding and plaque buildup than screw-retained-type prostheses.

Radiographic and clinical findings of the implants were observed during at least two follow-up appointments, which might explain the high survival rates in the short follow-up period. The short implant

follow-up time and not utilizing advanced statistical analyses, such as the Kaplan-Meier test, are among the limitations of this study.

Conclusion

Within the limitations of the study, the following conclusions can be drawn:

1. In all prosthesis planning compared in the study, more bone loss was observed around the distal implant than around the mesial implant.

2. Although it was not statistically significant, cemented-type prostheses had more marginal bone loss than screw-retained-type prostheses due to the repeated disconnections and reconnections of abutments during prosthetic treatment. Peri-mucositis clinical findings were mostly seen in cemented-type prostheses.

3. The results suggest that the two-unit splinted on two implants can preserve the marginal bone level. The increase in bone loss in the prosthetic superstructure planned with pontic may be due to the fact that oral care cannot be easily maintained there.

Ethics

Ethics Committee Approval: This retrospective clinical study was carried out at Uşak University with ethical committee approval number 41-11-20 (date: 22.07.2020).

Informed Consent: All patients were informed and included in the study after obtaining their consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: G.P., Design: G.P., Supervision: G.P., Materials: G.P., Data Collection or Processing: M.Ü., Analysis or Interpretation: M.Ü., Literature Search: G.P., C.G.K., Critical Review: C.G.K., Writing: G.P., C.G.K., M.Ü.

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Original Article / Özgün Araştırma

Awareness, Attitudes and Behaviours of Medicine, Dentistry, Nursing and Midwifery Students on Eye Health: A Cross-sectional Study

Tıp, Diş Hekimliği, Hemşirelik ve Ebelik Öğrencilerinin Göz Sağlığı Konusunda Farkındalık, Tutum ve Davranışları: Kesitsel Çalışma

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Abstract

Objective: Increasing ones' knowledge level of eye health for preventive medicine and early treatment is essential. This study aimed to identify students who completed their second year of health education and students in their final month of education as regards their awareness, attitudes and behaviours about eye health, to determine their approach to medicine and to draw attention to the shortcomings of education.

Materials and Methods: A face-to-face questionnaire survey was performed to 337 second-year volunteers and to medicine, dentistry, nursery and midwife students in their final year of education. Data collected were evaluated by descriptive statistics and chi-square test.

Results: Students' response rate was very low (76.2%-10.1%), even if they voluntarily participated to the survey (27.8%). They do not know about some of the basic knowledge such as uses of sunglasses, retinopathy of prematurity and coexistence of eye pathology in chronic diseases. They were not aware of the mandatory training on "rational drug treatment" in their curriculum. Although it is not legally possible, all students said they suggest accessibility of medications including antibiotics to people if they think they should use it.

Conclusion: Inadequate knowledge and misbeliefs on eye health among health care students were remarkable, which imply reconsideration of the educational curriculum. The suggestion rate of medications and beliefs on non-medical products were concerning. A general examination before graduation can help tackle this problem.

Öz

Amaç: Göz sağlığı konusunda bilgi düzeyinin artırılması hem koruyucu hekimlik, hem de erken dönemde tedaviye olanak vermesi yönünden oldukça önemlidir. Sağlık alanında eğitimlerinin ikinci yılını tamamlayan ve eğitimlerinin son ayına

gelmiş öğrencilerin göz sağlığı konusundaki tutum ve davranışlarını belirlemeyi, ilaçlara yaklaşımlarını tespit etmeyi ve eğitimin eksik kalan yönlerine dikkat çekmeyi amaçladık.
Gereç ve Yöntemler: Tıp, diş hekimliği, hemşirelik ve ebelik fakülteleri 2. ve son sınıfta eğitimlerini tamamlamakta olan toplam 337 gönüllü öğrenciye yüz yüze görüşme metoduyla anket uygulandı. Sonuçlar tanımlayıcı istatistik ve ki-kare testi ile değerlendirildi.
Bulgular: Gönüllü olarak ankete katılmayı kabul etseler bile (%27,8), öğrencilerin sorulara cevap verme oranları oldukça düşüktü (%76,2 ile %10,1 aralığında). Güneş gözlüğünün kullanımı, prematüre retinopatisi, kronik hastalıklarda göz tutulumu gibi bazı temel bilgiler bilinmiyordu. Ders programlarında olan "akılcı ilaç kullanımı" zorunlu eğitiminin farkında değillerdi. Hukuksal olarak uygun olmasa da, tüm öğrenciler antibiyotikleri dahi çevrelerindeki kişilere kullanılmasını uygun gördüklerinde önerdiklerini bildirmişlerdir.
Sonuç: Tüm öğrencilerin göz sağlığı konusunda yetersiz ve yanlış bilgileri dikkate değer olup, eğitim programları yeniden gözden geçirilmelidir. İlaçların önerilme oranı ve ilaç dışı ürünlere olan inanç endişe vericidir. Mezuniyetten hemen önce yapılacak genel bir sınav problemin çözümü için yardımcı olabilir.

Introduction

Education on preventive medicine is highly important in all fields of medicine as well as in ophthalmology (1). Thus, the prevalence of eye diseases like retinopathy of prematurity, cataracts can be reduced and possible complications like glaucoma, blindness can be prevented. With this we contribute to protect public health and reduce the budget allocated to treatment expenditures. Regardless of the socio-economic status of countries, cataracts, uncorrected refractive errors, glaucoma, age-related macular degeneration, and diabetic retinopathy are among the leading causes of blindness at the age of fifty and above (2). While cortical blindness, optic nerve abnormalities, retinopathy of prematurity, and cataracts are the leading causes of childhood blindness in developed countries; nutritional and infectious corneal opacities, cataracts, and premature retinopathy in developing and underdeveloped countries (3,4). In a study in Turkey, the rate of blindness in childhood due to preventable and treatable diseases is as high as 69.9% (5).

Following the studies on "rational drug use" initiated by the World Health Organization (WHO) in 1994, T.C. The Ministry of Health, Turkey Pharmaceuticals and Medical Devices Agency of Turkey Pharmacovigilance Agency (TÜFAM) operating in the Directorate General after 2000 has given importance to rational drug use (6). The clinician has the responsibility to diagnose the disease, determine the treatment goals, choose a reliable and efficiently proven treatment, write prescriptions without mistakes, start the treatment by giving relevant instructions to the patients, follow the treatment and perform rational drug administration (6). The patient also has responsibilities of understanding the importance of his disease, applying his treatment correctly, using drugs correctly, and taking protective cautions. Any deficiency in one of these stages could deteriorate the effectiveness and safety of the treatment; medical errors can harm the patient and lead to the increase of expenditures in treatments (1).

Students who are studying in the fields of health such as medicine, dentistry, nursing, and midwifery can provide consultancy to patients in eye diseases as well as in all health problems, even before their graduation. When necessary, it is extremely important for the students to refer the patients to the clinician for early diagnosis. With their knowledge, beliefs, attitudes, and behaviors in terms of preventions of eye diseases, they can play an important role in preventive medicine for both their own eye health and people around them. On the other hand, awareness of the undergraduate of health sciences about conveying the necessary and information in a correct way about doctor's prescription, usage and side effects of the drugs, also not recommending any medication, prescription of drugs considering that this is out of their competence and that they have not yet had doctor-patient training could be a very important factor that will directly affect the success of treatment.

The aim of this study is to determine the roles of students in the rational use of drugs, level of knowledge, awareness, beliefs, attitudes, and behaviors in order to protect eye health as well as to draw attention to the missing points in medical education concerning eye health and the rational use of drugs.

Materials and Methods

The presented study is a cross-sectional survey study and the universe of the study were students of medicine, dentistry, nursing, and midwifery faculties

who are completing the second year and final year of education at Aydın Adnan Menderes University. The questionnaire was applied to 2nd year students considering that the first year is the starting of the university and that the uncertainty about profession decreases at the end of the second year, their awareness, attitudes, and behaviors start developing in their profession. Thus, better participation in the survey and they could be more careful in their answers. Since students voluntarily participated in the survey, no signed consent form was needed. In addition, with this application, we ensured that the students participating in the survey are above 18 years old. The survey was applied to the final year students because they have more knowledge, awareness, attitude, and behavior of their occupations. Since the aim of this survey is to evaluate the knowledge and awareness levels, attitudes, and behaviors of the students that will start working after graduation that will take place a month after the survey.

The study was conducted with volunteer students at the cafe, reading rooms of the faculties, and amphitheaters of the university between 6-18 May 2019 (n=337). The Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University approved the survey (protocol no: 2019/74, date: 25.04.2019) and the permissions were obtained from the Deans of the Medicine, Dentistry, Nursery, and Midwifery Faculties. The questions of the survey were compiled from the literature review.

The volunteers were evaluated in 3 parts. At first, the socio-demographic data like age, gender, education, and questioning frequent ocular problems like refraction error, dyschromatopsia, and existing ocular disease. The second part included the basic level of knowledge and data sources of students. In order to evaluate the aforementioned data, there are several questions like:

From which eye disease does sunglasses protect?

In which chronic diseases does ophthalmic involvement occur?

Write two of them, write down one of the eye diseases in premature newborns?

Write down a contagious eye disease?

Write one of a precaution that comes to mind to protect your eye health?

How often should a routine eye examination be performed?

Did you receive rational drug training?

Which institution do you report the adverse effect of the drugs?

Select the source of information you use to get information about eye health, In addition, in this section, students were asked to grade from 1 to 5 on their own knowledge about drugs (1: Very bad, 2: Bad, 3: Medium, 4: Good, 5: Very good). They were asked how they perceive themselves about the route of administration, pharmacological properties, indications, side effects, contraindications, interactions (drug/nutrient), bioequivalence of drugs, and drug use in pregnancy or childhood. In the third part, there were questions to determine the belief, attitudes, and behavioral characteristics of the students. The related questions were:

Do you use sunglasses?

Do you use protective glasses during risky conditions?

Do you believe that reading books is harmful to the eyes?

Do you think devices such as mobile phones and tablets cause eye disease?

What is your trust rank in healthcare professions?

What do you think about products licensed by the Ministry of Food, Agriculture, and Livestock of Turkey (TCGTHB legal abbriviation in Turkish)?

What are your thoughts on imported drugs?

Do you recommend drugs for eye diseases?

Which drugs do you use and recommend most?

Since the students did not answer every question given in the questionnaire, the answers were evaluated not according to the number of questionnaires distributed in the classroom, but giving a proportion of answers to every question itself.

Statistical Analysis

The data were analyzed with the SPSS (version 21) statistical package program. Descriptive statistics of quantitative variables are expressed as mean ± standard deviation, and qualitative variables are expressed as frequency (percentage). Chi-square analysis was used for the independent analysis of qualitative variables. Values of $p<0.05$ were considered statistically significant.

Results

Socio-demographic Findings

All the data of the 337 participants were given in Table 1.

Fifty-five (23%) in a total of 240 students in the 2nd year of Medicine (MED2); 39 (22.3%) of 175 of 6th year medical students (MED6) participated in the study. The number of dentistry 2nd year (DEN2) was 38 (33%) out of 115 students, while 5th-year dentistry (DEN5), only 6 of 18 accepted to participate in our survey. Of 288 nursing students of 2nd (NUR2) and 202 students 4th year (NUR4) 46 (16%) and 71 (35.1%), respectively, took part in our study. Sixty two students (66%) out of 90 students in midwifery 2nd year (MID2) and 20 (24.1%) out of 83 students in the 4th year of midwifery (MID4) participated in our study.

The distribution of the students were as follows; 94 (27.9%) of the students in medicine, 44 (13.1%) in dentistry, 117 (34.7%) in nursing, and 82 (24.3%) in midwifery faculty. Of all the participants, 217 (64.4%) were female and 120 (35.6%) were male and the average age was found to be 21.5±1.8 years old. Three hundred and thirty-three students in total answered the question "Do you have any eye diseases?" 34 students (10.1%) answered the question "yes"; some of them had keratoconus, cataract, and allergic eye diseases. The refraction error was frequent (51.6 %) among students and most of them were myopic (27.6%). Refractive errors were corrected by using glasses 109 (71.7%), 23 (15.1%) lenses, and 18 (11.8%) glasses & lenses together. One of the students of MED6 had a laser operation for his myopia. None of the students had dyschromatopsia among the ones who had color vision examination (51.8%).

Level of Knowledge on Eye Diseases and Sources of Information The Students Refer to

Participation in the questions of this section and evaluation results for each class are shown in Table 2. It was remarkable that the students did not fill the questions requiring further information.

Table 1. Descriptive statistics of all participant's socio-demographic variables and educational background

Socio-demographics	Education							
	MED2	MED6	DEN2	DEN5	NUR2	NUR4	MID2	MID4
Age	20.7±1.3	24.5±1	20.4±0.9	23.2±0.4	20.2±0.7	22.6±1.2	20.1±1	22.2±0.7
Sex								
Female	25	19	20	5	28	41	60	19
Male	30	20	18	1	18	30	2	1
Eye disease								
Yes	6	13	7	0	1	6	1	0
No	49	26	31	6	45	65	59	20
Refractive errors								
No	21	10	11	3	27	36	34	7
Myopic	15	17	8	1	10	16	13	5
Hypermetropic	0	2	0	0	0	1	1	0
Astigmatism	0	1	4	0	1	2	0	0
Myopia-astigmatism	14	7	11	1	7	10	5	7
How do you correct the refractive errors?								
Glasses	20	15	15	0	17	21	15	7
Lens	8	4	2	1	1	4	1	2
Laser	0	1	0	0	0	0	0	0
Glasses + lens	1	5	4	1	0	3	4	0
Color vision test								
Examined	29	27	21	3	15	36	33	7
Not examined	23	11	17	3	31	35	28	11

MED: Medicine, DEN: Dentistry, MID: Midwifery, NUR: Nursing

Table 2. The students' knowledge, awareness about eye health as well as preferable reference or source of information, according to educational background

	Level of education							
	MED2	MED6	DEN2	DEN5	NUR2	NUR4	MID2	MID4
Write a disease that can be prevent with sunglasses								
Right/wrong	3/9	8/11	3/15	-	6/16	7/18	1/23	2/5
During the course of which chronic diseases eye involvement occurs								
1 Right/2 right/wrong	12/3/0	14/22/0	4/7/4	2/3/0	7/29/2	24/28/3	11/16/2	4/4/2
Write any eye disease seen in premature newborn								
Right/wrong	5/4	19/10	4/5	0/1	3/7	8/17	9/7	9/2
Write down any contagious eye disease								
Right/wrong	11/3	25/5	6/1	-	8/6	14/11	11/7	6/1
Write down what you know about the prevention of eye diseases								
Right/wrong	37/1	24/3	26/7	4/0	30/8	45/7	40/7	9/6
How often should the routine eye examination be performed?								
Every 6 months	29	14	25	3	17	36	34	9
Every 12 months	13	17	11	2	24	26	22	9
Every 2 years	5	4	1	1	3	6	3	2
Every 3 year	3	2	0	0	0	0	0	0
Have you received training on the rational use of drugs?								
Yes/No	14/39	33/6	5/32	6/0	11/34	25/45	47/15	16/1
To which institution do you report the adverse effect of the drugs?								
Right/Wrong	4/16	24/11	2/22	0/5	5/35	15/44	6/49	1/14
What are your sources of information for eye health and medications?								
Computer software (RxPharma®)	1	1	1	1	1	1	1	1
Friend	5	7	6	2	4	4	3	1
Book	7	17	2	1	9	20	4	1
Internet	22	18	19	3	25	33	18	4
Lecture notes	6	11	1	2	6	10	4	2
Optician	14	3	9	-	8	8	7	4
Pharmacy	10	1	6	2	6	9	11	8
I don't need	2	4	1	-	1	1	-	-
Doctor	40	22	25	5	33	56	58	18
Level of knowledge of the drugs route of administration	3.2±1.1	3.2±0.8	3.5±1.3	3.6±0.5	3.9±0.8	4.0±0.7	3.6±0.8	4.2±0.5
Level of knowledge of drugs pharmacological properties	2.7±1.1	3.0±0.7	2.9±1.2	3.4±0.5	3.4±1	3.2±0.8	3.1±0.7	3.1±0.6
Level of knowledge of drugs indications	2.6±1.1	3.4±0.7	3.1±1.2	4.0±0.7	3.2±0.9	3.3±0.7	3.1±0.6	3.3±0.7
Level of knowledge of drugs side effects	2.7±1.1	3.1±0.6	2.9±1.2	3.6±0.5	3.1±0.9	3.1±0.7	3.1±0.6	3.4±0.6
Level of knowledge of contraindications of drugs	2.4±1.1	3.0±0.7	2.6±1.4	3.6±0.5	3.0±0.9	3.2±0.7	2.9±0.7	3.5±0.6
Level of knowledge of drug interactions	2.5±1.1	2.8±0.9	2.8±1.2	3.4±0.5	3.1±0.9	2.9±0.8	3.0±0.7	3.3±0.7
Level of knowledge of drugs administration in special situations	2.4±1.0	2.7±0.8	3.1±1.1	3.6±0.5	3.1±1.0	3.1±0.9	3.3±0.8	3.6±0.7
Level of knowledge of drug bioequivalence	2.3±1.1	2.6±0.8	2.9±1.3	3.0±0.0	2.8±0.9	3.0±0.8	3.0±0.8	3.1±0.7

MED: Medicine, DEN: Dentistry, MID: Midwifery, NUR: Nursing

Those who answered the question "Which disease do sunglasses protect?" Such as cataracts and cancer are correct, and those who say they do not protect are considered incorrect answers. 82.9% (76 people) of all 2nd-year students who participated in the survey gave the wrong answers to this question, MID2 group had the highest percentage of wrong answers; only 1 out of 24 students could answer correctly. It was surprising that most students about to start professional life did not answer, and 66.7% of the respondents gave wrong answers.

When we asked the students to give any two examples to the question of which chronic diseases have ocular involvement during their course (hypertension, diabetes, an endocrinological or rheumatological disease), the total number of students who answered the question was 203. NUR2, NUR4, MID2, and MID4 students wrote answers such as miosis, rash, dryness. Although there were no incorrect answers in the MED2 and MED6 groups, we found that the rates of double correct answers were low (20% and 61.1%, respectively).

We observed that a total of 110 students answered the question "What kind of eye disease develops in a premature newborn?". Considering that there are 337 students participating in the questionnaire, 2/3 of the students could not answer this question. While we accepted answers such as blindness, strabismus, refractive error, and ophthalmopathy/retinopathy as correct, we considered responses such as color blindness, stye, and jaundice as wrong answers. Fifty-seven out of 110 gave correct answers (51.8%).

One hundred fifteen students responded to "Write down a contagious eye disease" and 81 out of 115 gave correct answers (70.4%) such as conjunctivitis. However, there were wrong responses like redness, glaucoma, and miosis.

Two hundred fifty four students responded to the question "Please write something that comes to your mind to protect your eye health"; 215 of these students (84.6%) said "I pay attention to my nutrition, my sleep, I use glasses" and their answers were accepted as correct. Ambiguous answers such as "I go to the doctor, I take care of my eye"" were considered incorrect. The MID4 group, among which 15 people answered this question had 60%, being the least correct answer rate.

Another question including eye health was "How often should a routine eye examination be done?" 167 (52.0%) out of 321 marked "once in 6 months", and 124 (38.6%) "once a year". Those who marked the option every 2 years or 3 years were in the minority.

All of the students (n=239; MED6, DEN5, NUR2, NUR4, MID2, and MID4) except MED2 and DEN2 stated that they received courses, medical pharmacology, and treatment training during their education as a response to the "Have you received training on rational drug use?" question. Despite this, 44.6% (111 people) declared that they did not receive rational medicine training. 47.7% of the 239 students stated that they received this training from the curriculum or at the congresses they attended.

Two hundred fifty three students responded to "Which institution do you report the adverse effect?", only 57 of them (22.5%) were able to give the "TÜFAM" correct answer. Answers such as "to the WHO and the pharmaceutical company" were considered incorrect. Of the 35 MED6 students who answered this question, only 24 of them were able to give the "TÜFAM" correct answer.

When we asked the students about their sources of information, the response rate was high. All students who selected several options at the same time chose the options "I ask the doctor" with a maximum of 257 answers and "I check from the internet" with 143 answers. Seven students stated that they use a computer software program (RxMedia®), 9 students stated that they do not need to ask and 32 students preferred to ask their friends.

We asked students to rate themselves between 1 (very poor) and 5 (very good) points for their level of knowledge about drugs. The MID4 and NUR4 groups gave 4.2±0.5 and 4.0±0.7 points to themselves regarding the route of administering the drugs, the MED2 and MED6 groups gave 3.2±1.1 and 3.2±0.8 points to themselves. The DEN5 (3.4±0.5) and NUR2 (3.4±1) groups found themselves in the best position regarding the pharmacological properties of the drugs. NUR4 (3.2±0.8), MID2 (3.1±0.7) and MID4 (3.1±0.6) students rated themselves more knowledgeable than MED6 (3.0±0.7). Six students in the DEN5 group (4.0±0.7) and those in the MED6 (3.4±0.7) group gave themselves high scores in terms of their knowledge on the indications of drugs followed by NUR4 (3.3±0.7) and MID4 (3.3±0.7) students. Evaluating themselves

about the side effects of drugs, 6 students in the DEN5 group (3.6±0.5) and those in the MID4 (3.4±0.6) group gave high scores themselves. MED6, NUR2, NUR4, MID2 scores were similar to 3.1. Six students in the DEN5 group (3.6±0.5) and those in the MID4 (3.5±0.6) group gave themselves the highest score about the contraindications of the drugs. Among the students who scored their knowledge on drug interactions, 6 students from the DEN5 group (3.4±0.5), the MID4 group (3.3±0.7) gave higher points to themselves higher than the MED6 group (2.8±0.9). When we evaluated the administration of drugs to patients with special conditions, 6 students in the DEN5 group (3.6±0.5) and the MID4 (3.6±0.7) group scored themselves high, leaving MED6 students (2.7±0.8) behind. In terms of drug bioequivalence, MED2 (2.3±1.1) and MED6 students (2.6±0.8) got the lowest score, while all other groups gave themselves higher scores than MED students, regardless of differences in the year of study. In almost all evaluations, the scores from NUR2, NUR4, MID2, and MID4 students were above the average number (3), and in some questions, it was higher than MED6 students.

Belief, Attitude, and Behavior Characteristics

Answers to the questions of this section as well as results for each year and education background are shown in Table 3. Sixty-six (19.6%) students answered yes, 176 students (52.2%) answered sometimes and 95 students (28.2%) answered no to the question "Do you use sunglasses?". The highest rate of sunglasses use was among the MED6 group with 13 (33.3%). A total of 155 students (46.7%) answered yes, while 177 (53.3%) answered no to the question "Do you use protective glasses for risky jobs?". Five students in DEN5 (83.3%) and 24 students in DEN2 (64.9%) groups protect themselves in risky jobs most among other groups, while those who protect the least are the MID2 group (18 people, 29.5%) and the MID4 group (7 people, 35%). A total of 130 (39%) participants said yes, while 203 (61%) answered no to the question, "Is reading a book harmful for eyes?". Those who believed that reading books are harmful to the eyes were the NUR4 group with 33 (46.5%) and MED6 with 18 (46.2%). Those who believed that reading books do not disturb the eyes were 47 students in the MID2 group, saying no with 75.8%.

Three hundred thirteen students (93.2%) answered yes and 23 students (6.8%) answered no to the question "Do you think using mobile phones and tablets causes eye disease?". The MED6 group has the highest rate with 6 students responding no to this question (15.4%).

When we asked about their beliefs/trust in the professional groups in eye health and asking to rank out of 5 points, the most trusted group was ophthalmologists scoring between 4.7 and 5. In the second-rank, unlike all other students, 3 points were given to nurses at NUR2 group students, family physicians (2.7 points) were less trusted than nurses (3 points) on eye health.

We asked the students about their beliefs about TCGTHB approved products and drugs from abroad. The opinion about whether the products approved by the TCGTHB are more effective than drugs was not statistically different between the study groups (p=0.084). Two hundred forty two (80.1%) out of 302 students who answered this question thought that the products approved by TCGTHB were not more effective. Students of MED6 group stated that they found these products less reliable than drugs, unlike other groups (MED2, NUR2, NUR4, and MID2), with a rate of 94.9% (p=0.003). Six students from the DEN5 group also found these products unreliable. A hundred twenty three (40.6%) of all students believed that these products had fewer side effects than drugs, MED6 group students did not agree with this point of view with a rate of 94.9% and made a difference compared to all other groups (p=0.001). Ninety four students (30.9%) shared the opinion that TCGTHB approved products are suitable for most patients, while according to 210 students (69.1%) they would not be suitable (p=0.004). MED6 group students agree with 94.9% of the opinion that these products are not suitable for most patients. All student groups (302 students) agreed with 70.5% that the products will reduce the cost of treatment due to fast and precise treatment (p=0.248). The MED6 group students who found these products unreliable at a rate of 94.9%, stated that the side effects were not less than the drug and that they would not be suitable for most patients agreed with the idea that they could reduce treatment costs by 58.3%.

The students (n=309) had different opinions according to their years of study on whether or not the drugs from abroad are more effective. In general, 49.8% overall agree that it is more effective. While

MED2 said that it was 63% effective, MED6 agreed also at a rate of 40.5%. They declared that they find these drugs effective at the following rates; DEN2 79.4%, DEN5 60.0%, NUR2 59.1%, NUR4 35.8%, MID2 36.7% and MID4 50.0%. In comparison between group results on the effectiveness of drugs from abroad; MED2 is different from MED6, NUR4, and MID2; MED6 is different from DEN2; DEN2 found different from NUR4 and MID2 ($p<0.001$). The rate of those who found the drugs from abroad more reliable was 34.6%. There were statistically significant differences between groups and these are as follows; MED2 and

Table 3. The student's belief, attitude and behavior according to their educational background

Education	MED2	MED6	DEN2	DEN5	NUR2	NUR4	MID2	MID4	p
Do you use sunglasses?									
Yes	13	13	8	2	8	13	8	1	-
Sometimes	25	19	19	3	21	45	32	12	
No	17	7	11	1	17	13	22	7	
Do you use protective glasses for works with risks?									
Yes/no	25/29	20/17	24/ 13	5/1	21/25	35/36	18/43	7/13	-
% of yes	46.3	54.1	64.9	83.3	45.7	49.3	29.5	35	
Do you believe that reading book can cause damage to the eye?									
Yes/no	23/30	18/21	15/23	2/4	16/29	33/38	15/47	8/11	-
Do you think devices like mobile phones and tablets cause eye disease?									
Yes/no	51/4	33/6	35/2	6/0	43/3	66/5	61/1	18/2	-
Confidence index									
To the pharmacy	2.5±0.8	2.5±0.8	2.2±0.8	2.1±0.7	2.3±0.9	2.2±0.8	2.3±0.8	2.5±1	-
To the family doctor	3.2±1.0	3.4±0.8	3.2±1	3.3±0.8	2.7±0.8	3.0±1	3.0±0.8	2.8±1	
To the nurse	2.2±0.8	2.2±0.8	2.1±0.5	1.8±0.5	3.0±0.9	2.8±1	2.3±0.9	2.3±0.7	
To the ophthalmologist	4.8±0.6	4.9±0.5	4.9±0.5	5±0	4.8±0.6	4.7±0.7	4.8±0.5	4.8±0.2	
To the optician	2.3±0.9	2.1±0.9	2.7±1	2.8±0.8	2.2±1	2.3±0.9	2.5±1	2.6±1.1	
TCGTHB approved drugs are more effective T/F	10/31	1/38	5/30	0/5	12/31	15/51	14/44	3/12	0.084
TCGTHB approved drugs are safer T/F	10/32	2/37	7/28	0/5	9/35	25/42	22/36	3/12	0.003
TCGTHB approved drugs have fewer side effects T/F	17/24	2/37	19/16	2/3	20/23	29/38	28/30	6/9	0.001
TCGTHB approved drugs are more favorable T/F	11/30	2/37	14/21	0/5	15/30	22/45	25/32	5/10	0.004
TCGTHB approved drugs are cheaper T/F	32/11	21/15	29/6	3/2	36/9	45/20	37/20	10/6	0.248
Imported drugs are more effective T/F	29/17	15/22	27/7	3/2	26/18	24/43	22/38	8/8	<0.001
Imported drugs are safer T/F	19/26	14/23	20/14	2/3	19/25	15/53	11/49	7/9	0.001
Imported drugs have fewer side effects T/F	6/39	9/29	11/23	2/3	14/30	12/54	10/50	4/12	0.240
Imported drugs are more favorable drugs T/F	20/26	10/27	11/22	1/4	17/25	21/45	16/44	6/9	0.575
Imported drugs are cheaper T/F	18/26	8/29	13/21	2/3	19/25	26/40	15/45	6/10	0.304

TCGTHB: The Republic of Turkey, Ministry of Food Agriculture and Livestock, MED: Medicine, DEN: Dentistry, MID: Midwifery, NUR: Nursing, T: True, F: False

NUR4 differ from MID2; MED6 differ from MID2; DEN2, NUR4 differ from MID2; finally NUR2, NUR4 differ from MID2 group (p=0.001). 77.9% of these students disagreed with the idea that drugs from abroad have less side effects (p=0.240) and 66.4% stated that it was not suitable for most patients (p=0.575). Only 35% of all students (306 students) thought that drugs from abroad would reduce the cost of treatment due to rapid and definitive treatment (p=0.304).

When the students were asked whether they would recommend medication to their relatives in case of any eye disease; in all groups, positive responses were 8.3% (p=0.084). The distribution of positive responses according to groups was as follows: MED2 13.7%, MED6 23.7%, DEN2 2.9%, NUR2 8.9%, NUR4 7%, MID2 1.6%. Although 91.7% of all students answered no to the above mentioned question; then the question "Which group of drugs do you recommend for eye diseases?" they recommended medications like pain killers, antibiotics, vitamins, and anti-allergic drugs and marked one or more of these drugs (Table 4). The most recommended drugs were an anti-allergic and antibiotic group of drugs.

Discussion

Precautions concerning eye health and wise approaches are important to prevent lifetime damages to the eye. However, sometimes insufficient information, false beliefs, and practices can be harmful. When the midwife, nurse, or family physician fails to provide guidance or refer the patient in situations like premature retinopathy, one of the most important eye emergencies, the patient can develop retinal detachment, angle-closure glaucoma, and painful absolute blindness in both eyes. Dentists, nurses, and midwives need to have as much information as family physicians about diseases that can cause blindness such as retinopathy of prematurity, diabetic retinopathy, and glaucoma to make the patient reach ophthalmologists for early diagnosis and treatment. Because all healthcare professionals can be placed in many different units, as it is happening during the pandemic of coronavirus disease-2019, they are expected to have sufficient knowledge not only in basic concepts like rational use of drugs but also in subjects that require expertise mainly emergencies and diseases that may cause acute blindness.

51.6% of the students had refractive errors, the most frequent was myopia with 27.6%. As expected, most of the students use glasses to correct the refractive error. In similar two studies, 56.9% of medical faculty students had refractive errors, of which myopia (63.3%) was the most frequent (7,8). In another study conducted in our country among medical faculty students, 32.9% were found to have myopia (9). This situation is a very big concern because as in our study, even the fact that it was performed only in a certain community, refractive error emerging in half of the community in these studies. According to a study published in 2016, half of the world population will be myopic in 2050 (10). However the previously mentioned studies show that this prediction is almost a reality before 2020.

Netto et al. (11) reported that medical faculty students were evaluated with the Ishihara color vision tests, the rate of dyschromatopsia was found

Table 4. Participants drug recommendation for eye diseases according to their educational background

Educational background	MED2	MED6	DEN2	DEN5	NUR2	NUR4	MID2	MID4
Would you recommend any medication?								
Yes/no	7/44	9/29	1/33	0/5	4/41	5/66	1/61	0/19
Pain killer	4	11	9	-	11	11	6	1
Antibiotic	6	14	4	-	11	16	9	4
Drugs for the common cold	2	4	1	-	-	5	-	-
Vitamins	2	2	6	-	7	8	4	-
Drugs for allergy	11	15	12	-	19	14	20	4
Eye drop	0	0	1	-	2	0	1	0

MED: Medicine, DEN: Dentistry, MID: Midwifery, NUR: Nursing, *Students who wrote eye drop was mentioned separately since the prescribed drugs were not clearly mentioned (however, they chose the "no, I do not recommend drugs" option, a high percentage of students recommend one or more drugs)

to be 2.6% and 81.2% of these participants reported to have already been aware of this disease. In our study, 48.2% of the students, although have not been submitted to color vision tests stated that they did not have any defects. However, concerning this statement, even though they did not go to the ophthalmologist, they may have got aware of their situation after being submitted to tests by their family physicians to get a health report for school or driving license admission. For this reason, we think the rate of dyschromatopsia in our study is similar to the study of Netto et al. (11).

We asked simple questions to the students about daily life because we did not mean to transform the questionnaire into an exam but to assess for the level of knowledge and awareness. Despite this, the students' response rate was low. The students do not know the importance of sunglasses for eye health. We expected all of our students to know that ocular involvement may occur in the course of chronic diseases, and 60% of the 6th-year medical student's group were able to write two correct diseases. When asked about what kind of eye disease that develops in a premature newborn, 1/3 of all students wrote anything including jaundice and stye; only half of them could establish a relationship between preterm birth and diseases such as retinopathy, strabismus, and refractive errors. It is important to point out that medicine, dental, nursing, and midwifery students graduating in a month, do not remember or think about a serious disease such as retinopathy, which can be partially managed with early interventions. Some students were not able to write conjunctivitis as one of contagious eye diseases and did not recommend anything to protect the eye from diseases. They think that a routine eye examination should be performed every 6 months. In a study conducted with 196 family physicians in Ankara, 87.2% of the residents thought that the ophthalmology education provided in the medical faculty was insufficient (12), this percentage is very high and supports the results of our study. It is worrisome that healthcare professionals that will take part in primary care will not be able to respond to basic needs.

Considering the individual errors on the rational use of drugs, physicians, patients, nurses, and pharmacists have a very important role and responsibility (1,13). However, in our society, students who start higher education apart from being valued, are considered as a source of information in the field of health to the people around them. This situation may be due to the difficulty of the patients in accessing health services and or could be also related to the trust in their relatives or people they know. The level of knowledge of all these students is important not only in counseling but also because they can personally be sick. The Ministry of Health declared that 44.5% of the students did not receive the training of "rational drug use", which is a compulsory course of vocational training. This high rate suggests the need of reviewing the courses in the curriculum and increasing the number of courses related to the rational use of drugs. Students did not know TÜFAM and that it is the entity where we report adverse effects. Students mostly left the information questions about diseases of the eye, blank. For eye health and medications, they chose the "I mostly check from the internet" option as the source of information, and books remained among not preferred sources. In the questions about drugs, except for medical students, all the others claimed to have knowledge above-average regardless of the education year differences. Despite the advance in years of education, medical students feel less competent than midwifery and nursing students in terms of their level of knowledge, the reason may be because they have had the opportunity to test and evaluate themselves in different situations, as well as the opportunity approach patients in the clinical and outpatient clinics environment and therefore may have increased their awareness concerning this topic. We think that measuring the knowledge and awareness of nursing and midwifery students with an examination system at the end of the course, as in the specialty examination for medicine (TUS) would be good.

Our students could not give satisfactory answers to the question of eye disease that can be prevented with sunglasses. We would expect them to know that sunglasses can protect from excessive ultraviole in our geography causing cataract or pterygium, or to know that because of high cosmetic concerns nowadays, it can prevent wrinkles that may develop around the eyes, so the rate of using sunglasses would be higher (14-16). Glasses are also important among personal protective equipment (PPE) in dangerous or risky jobs. Although dentistry students attach the most to the

importance of its use, we found that these students graduated before they fully gained the habit of using PPE.

As advances in the year of education, there is an increase in the rate of beliefs that reading books is disruptive to the eye. On the other hand, 39% of all students believe that reading books, 93.2% of them believe that gadgets such as mobile phones and tablets damage the eye. Reading books and using digital displays such as mobile phones or tablets are both considered activities of near vision. Many publications suggest that these near vision activities also increase the frequency and degree of myopia (17-19). Concerning this, we can conclude that it is possible to conclude that our students' awareness is high.

The study found that students' trust in ophthalmologists was high, while last year nursing students trusted nurses more than family physicians.

We also questioned their attitude towards products approved by TCGTHB in this study. The number of students who say that these products are more effective and safer than the drugs approved by the Ministry of Health decreases rapidly as the years of education increase in medical and dentistry students. We also noticed that 20% and 37.3% of nursing and midwifery students graduate with beliefs that agricultural products are more effective and safer to use than drugs in treatment. While 5.1% of 6th-year medical students agree that these products have fewer side effects than drugs, as well as 40-43.3% of students from other faculties. Again, only 5.1% of 6th-year medical students agreed to administer these to patients, while 32.8-33.3% of other faculty students found it suitable.

Interestingly, when we look at all the students, 70.5% believe that TCGTHB approved products offer a cheaper treatment option. Although they say these products are ineffective and may have side effects, contradicting themselves, seeing them as a cheap treatment option. Some of the products sold in the market are more expensive than the drugs, but the most important is the cost of the treatment, not the price of the daily used drugs. The price of the drug in this case is like the tip of the iceberg. Many factors such as duration of treatment, possible side effects, and supportive treatments added to the cost of treatment. A non-therapeutic product may cause more waste of time and the existing disease to become more problematic, which will increase the cost. With similar questions, we wanted to evaluate the students' belief in imported drugs. With the increase in years of education, the belief of students that these drugs are more effective and safer decreased, still at the level of 35-40%. The belief that it has few side effects is 22.1%, and the belief that it is suitable for most patients is 33.6%. 35 percent of students think that the cost of fast and definite treatment was cheap.

In the study, even the second-year students of all faculties stated that they recommended drugs to their relatives. In our country, where the Ministry of Health gives importance to studies related to the rational use of drugs, considering that the authority to prescribe drugs for patients is only of medical doctors and dentists, administering or recommending medication by students may cause problems. Also important to notice that the use of antibiotics is also easily recommended. In our society, using drugs without consulting a physician is very common (1). Prevention of medical errors is important in terms of damages both to the patient and to the economic system; education concerning this issue should be reinforced during university education.

Conclusion

Considering the level of knowledge and education background on eye diseases and rational use of drugs among the students at the beginning and those at the end of the course and about to receive their diplomas in one month, most students were not able to answer even the simplest questions, and among those who answered there was a high and remarkable rate of mistakes were. To increase their level of knowledge about these topics, asking a doctor, and checking on the internet was a priority over books. Concerning their understanding of the importance of preventive treatment observing their attitudes and behaviors, we noticed that during the education years they have not sufficiently acquired good habits on the topic. Besides this, concerning the knowledge of drugs, regardless of the year of education, nursing and midwifery students scored themselves above-average. Parallelly, in that level of education, scoring themselves a high level of knowledge, most students recommend allergy and antibiotic drug groups to patients which is out of their competence and illegal. We think that especially for

nursing and midwifery students taking an exam like medical and dentistry students will be beneficial in terms of increasing their quality of education and training as well as benefits for the health-care of the society.

Ethics

Ethics Committee Approval: The Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University approved the survey (protocol no: 2019/74, date: 25.04.2019).

Informed Consent: Since students voluntarily participated in the survey, no signed consent form was needed.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.İ.A.Ü., B.D., Design: A.İ.A.Ü., F.J.L.J., B.D., Supervision: A.İ.A.Ü., B.D., Data Collection or Processing: A.İ.A.Ü., F.J.L.J., B.D., Analysis or Interpretation: A.İ.A.Ü., F.C., İ.K.Ö., A.Ü., B.D., Literature Search: A.İ.A.Ü., F.J.L.J., A.Ü., B.D., Critical Review: A.İ.A.Ü., F.J.L.J., İ.K.Ö., A.Ü., B.D., Writing: A.İ.A.Ü., A.Ü., B.D.

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Original Article / Özgün Araştırma

Effect of Non-cadaveric Methods on the Anatomy Education of Medical Students

Kadavra Dışı Yöntemlerin Tıp Öğrencilerinin Anatomi Eğitimine Etkisi

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Keywords
3D Human Anatomy Application, human anatomy, anatomy education, human anatomy models, medical education

Anahtar Kelimeler
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Abstract

Objective: Recently, with the inability to conduct face-to-face training due to the increasing cases of pandemic diseases such as the coronavirus disease-2019, the importance of digital applications in practical anatomy education has increased. This study aimed to compare cadaveric and non-cadaveric examination methods to evaluate the benefits of innovative models for education.

Materials and Methods: A total of 120 second-year medical student volunteers who had never used the three-dimensional (3D) Human Anatomy Application participated in the study. They were asked to fill out a questionnaire containing their opinions about the anatomy lesson. Then, the students were randomly divided into three groups according to their learning methods.

Results: Among the participants, 75.9% stated that working on the model was sufficient and 36.7% mostly used the printed human anatomy atlas when studying for practical lesson. While the success rates of different modules were similar in the practice groups, in the same module, the success of the 3D Human Anatomy Application group was higher than that of other practice groups.

Conclusion: Although they had not used it before, students who received training with the 3D Human Anatomy Application were more successful than the other groups. 3D applications developed in recent years have offered a new perspective to anatomy education by creating a sense of reality without touching it and allow formations and examinations from all angles. With the emergence of pandemic diseases, 3D applications will gain more importance as the future of anatomy education.

Öz

Amaç: Son yıllarda koronavirüs hastalığı-2019 gibi pandemik hastalıkların artmasıyla yüz yüze eğitimin yapılamaması anatomi uygulama eğitiminde dijital uygulamaların önemini artırmıştır. Gelişen teknolojinin yarattığı yenilikçi modellerin eğitime sağladığı yararları değerlendirmek için kadavra dışında kullandığımız yöntemleri kıyaslamak istedik.

Gereç ve Yöntemler: Çalışmamıza üç boyutlu (3D) İnsan Anatomisi Uygulaması'nı hiç kullanmayan 120 ikinci sınıf tıp öğrencisi gönüllü katıldı. Öğrencilerden anatomi dersi ile ilgili görüşlerini içeren bir anket doldurmaları istendi. Daha sonra öğrenciler öğrenme yöntemlerine göre rastgele üç gruba ayrıldı.

Bulgular: Anket sonucunda öğrencilerin %75,9'u maket üzerinde çalışmanın yeterli olduğunu, %36,7'si uygulama dersi için çalışırken en çok basılı insan anatomisi atlasını kullandığını belirtmiştir. Test sonucunda ise uygulama gruplarında farklı

ders kurulları arasında başarı benzerken, aynı ders kurulunda 3D İnsan Anatomisi Uygulama grubunun başarısı diğer uygulama gruplarına göre daha yüksekti.
Sonuç: Daha önce kullanmadıkları halde 3D İnsan Anatomisi Uygulaması ile eğitim alan öğrenciler diğer gruplara göre daha başarılı oldular. Son yıllarda gelişen 3D anatomi uygulamaları, dokunmadan gerçeklik hissi yaratarak ve oluşumların tüm açılardan incelenmesine olanak sağlayarak anatomi eğitimine yeni bir bakış açısı sunmuştur. Artan pandemik hastalıklar nedeniyle anatomi eğitiminin geleceğinde daha fazla önem kazanacağını düşünüyoruz.

Introduction

Human anatomy, which is the most important component of medical education, is the branch of science that examines the normal shape and structure of the body, the organs that make up the body and the relationships between them. Anatomy, which is taught theoretically and practically to students in the first years of medical school, is the cornerstone of medical education (1-3). In order for the students to learn the human body comprehensively, to train them more efficiently and to interpret the diagnosis and treatment of diseases clinically, the anatomy education should also be done practically. While seeing the structure of the human body during practical training allows them to learn in detail, their confrontation with the phenomenon of death contributes to the formation of a physician identity (4-6).

It is widely accepted that the ideal method for students to learn and understand human anatomy should be practical training as well as theory. Dissection has been the cornerstone of practical anatomy education for over 400 years (7,8). The dissection of human cadavers enables the person to be prepared for death, active and deep learning, to develop manual skills, and to understand the relationship between the symptoms and pathology of diseases (9-11). In addition, it teaches students to be respectful and attentive to the cadaver, and gives students an important ethical awareness in their approach to their patients in the future (4).

Today the resources for the cadaver need are the orphans, body donation and the import of cadavers from other countries, all arranged with legal regulations (12). There are countries in the world that provide the majority of cadavers through donations (13,14). However, for African countries Ethiopia, Kenya, Ghana and Nigeria, Asian countries Turkey, India, Indonesia, Iran, Saudi Arabia, Singapore, Bangladesh, European countries Bulgaria, Greece, Italy, Romania, Serbia, North American country Mexico, South American countries Argentina, Brazil, Colombia and Paraguay, the supply of cadaver is often from orphans and there is need for more donations (13).

Difficulties in obtaining cadavers worldwide limit their use in education. While countries such as Malaysia, Saudi Arabia, and Singapore try to get their cadavers from foreign countries because of the low amount of donations (15-17); donation in China is quite high, however still insufficient for the density of students (18,19). In our country, insufficient donation and high cost of imported material are the biggest obstacles in meeting the cadaver need (20).

The applications to the dead human body trigger the objection bacause of the social and traditional structure, morality and religion. Therefore, the relevant provisions of the laws allow the body to be used in scientific research after death and to protect it from all kinds of malicious situations. According to the regulated laws [Article 14 (6) Law on Organ and Tissue Collection, Preservation and Transplantation Dated 1979 Numbered 2238], a person can donate his body as a cadaver with his will or with the approval of his relatives after death (21,22). In our country, efforts are made to raise public awareness by informing about the protection of donation by laws and how important the benefits it will bring to science are (18,21,23,24).

For anatomy education, the average number of students per cadaver should be between 4-12. It has been reported that our country has an average above this number and that there are no cadavers in some universities that teach anatomy (21). Apart from the difficulties of supplying cadavers in universities, there are also problems such as suitability of dissection laboratories (space and ventilation problems suitable for the number of people) and high costs associated with their maintenance and inadequate number of cadavers compared to the increasing number of students in most medical schools. In addition, with cadaver dissection in which students actively participate, education takes a long time;

also, inaccessibility to some body parts, change and destruction of the organs and tissues of the cadaver in time and the negative effects of exposure to formaldehyde smoke may impair the quality of education (25-28). By saying that "to obtain a true and perfect knowledge of which (some few veins) I have dissected more than ten human bodies", Leonardo da Vinci emphasized that understanding the human body by dissection requires intense effort (29). The increasing number of pandemic diseases in recent years, make cadaver training impossible (30,31). Pather et al. (32) also stated that after the coronavirus disease-2019 (COVID-19) epidemic, anatomy education stepped into an unknown future. These reasons led anatomists to seek new educational tools (33).

Developing technology creates new opportunities in education as well as in many other fields. In recent years, the use of some technological materials in anatomy education has increased significantly. The main purpose of alternative learning tools developed in this area is to avoid the negative aspects of cadaver education and to create materials close to it (34,35). Today's innovative digital technologies increase the effectiveness of anatomy learning by using lternative learning strategies and alternative education tools. Anatomy models and three dimensional (3D) Anatomy Apps developed each day are among the frequently used educational tools. Increased and visually enriched printed anatomy atlases also support education and learning (35,36). Plastination, use of 3D printed models and teaching of living and radiologic anatomy are among the other methods used in anatomy education (37).

In our faculty, combined education is given on human models and cadavers. Students, as extracurricular materials, use printed atlases and 3D Human Anatomy App in our university database. We wanted to investigate the effect of these methods, which we use as an alternative to cadavers, on learning.

Materials and Methods

Medical faculty students studying intensive anatomy at Aydın Adnan Menderes University were included in the study. The study was carried out with the participation of 120 volunteers (62 males, 58 females) from students who took a musculoskeletal system course in the first year of their education, passed the theoretical and practical exams and who have never used 3D Human Anatomy Apps in our university's database.

At the beginning of the school year, a questionnaire consisting of 5 questions was applied to the participants to evaluate their opinions about the anatomy lesson. While the students were only asked to indicate their age and sex in the content of the questionnaire, the students were not asked to write their names and surnames for the reliability of the answers. The following questions were asked: "Do you enjoy studying anatomy?", "Do you think it is sufficient to work on human models in anatomy practical lessons?", "Do you find the duration of anatomy practical lesson sufficient?", "Do you think that learning would be insufficient if cadavers were not used in anatomy practical lessons?" and "List the resources you used while studying anatomy lesson, from most to least (maximum: 1, medium: 2, minimum: 3)". In the answer to first four questions; a 5-point Likert-type scale consisting of "always", "mostly", "not sure", "occasionally", "never" was used and for the last question resources to be considered were listed as "Course Notes", "Human Models", Human Anatomy Atlases.

From anatomy practical education models used by students, current atlases (Human Anatomy Atlas), models in the practice hall of our university (Human Anatomy Models) and 3D digital visual anatomy program in the database (3D Human Anatomy Apps) were selected (Figure 1A). According to these educational models, students were randomly and equally distributed to 3 groups named as Human Anatomy Atlas group (AG), Human Anatomy Models group (MG) and 3D Human Anatomy App group (3DG).

Three modules were selected for our research, in which the practical education was very intensive. Among these, cranial nerve and peripheral nervous system anatomy from neuroanatomy, heart anatomy from the cardiovascular system, and stomach, small and large intestine anatomy from the digestive system were evaluated. First, the students were given a theoretical lesson on the subjects, and then a practical lesson was given according to their groups.

At the end of the lecture, 25 structures were randomly selected from each of the regions described. The first form containing a name table by encoding

the anatomical structures with letters, an empty answer table by encoding the same by numbers was distributed to the students (Figure 1B). Students were given the second form containing questions on the subject of the visuals of these selected anatomical structures, and they were asked to fill in the letters corresponding to the asked structures in the answer table (Figure 1C). Ten minutes were defined for each table containing 25 questions. Each question was evaluated as 4 points and the success scores of the students were calculated over 100. The whole study process is defined in Figure 2.

Statistical Analysis

The scores were transferred to SPSS for Windows release 11.0 for statistical analysis. Minimum, maximum, mean and standard deviation values of the data were determined and compared with practical education models and modules by One-Way ANOVA test. Statistical significance was considered $p<0.05$.

Results

In our study, the participating students were 20-22 years old; 62 (51.6%) were males and 58 (48.4%) were females. The results of the questionnaire are given in Figure 3.

In our study, the answers of the students were evaluated and the mean, standard deviation, minimum and maximum values according to the subjects and groups are given in Table 1.

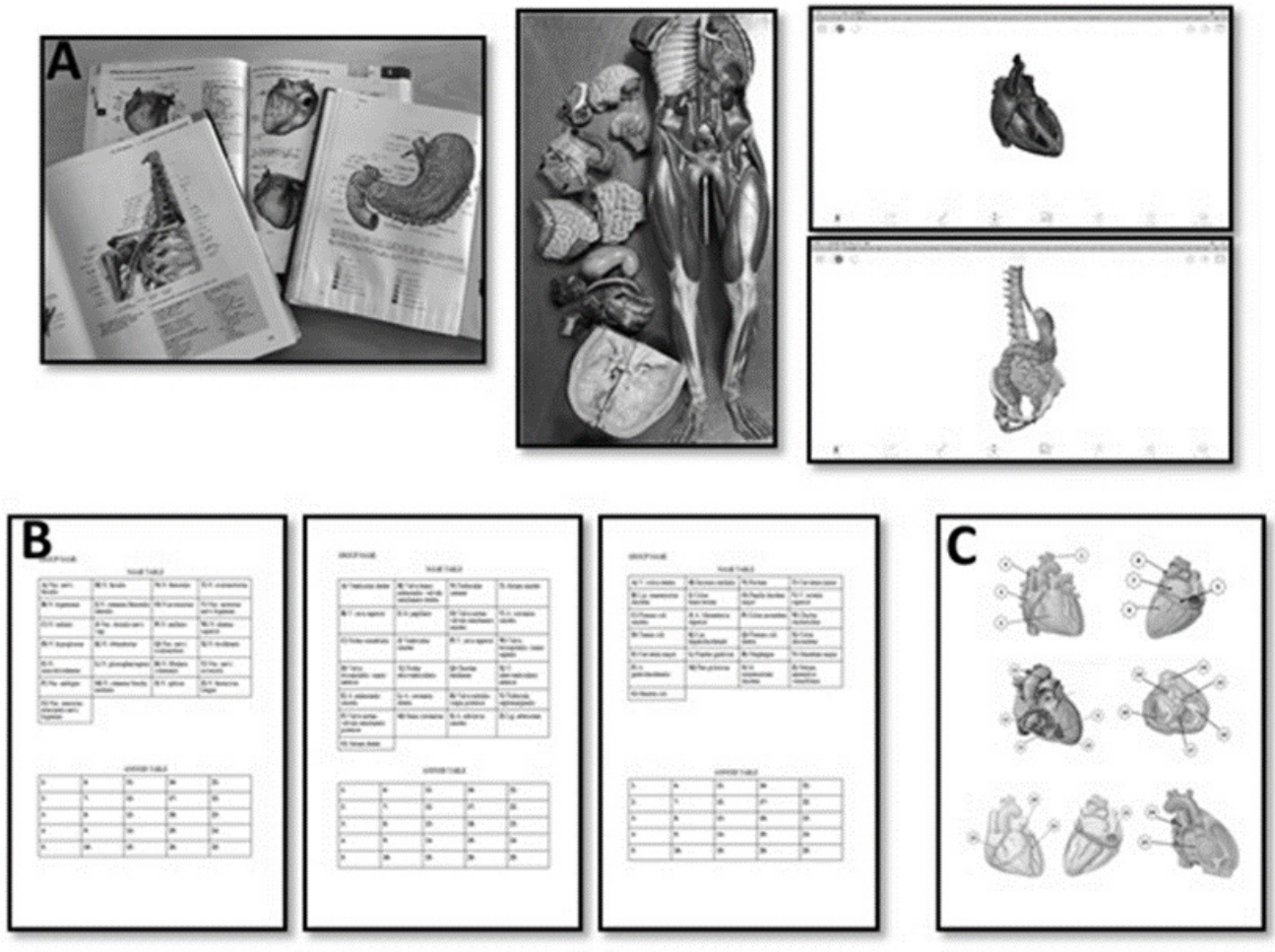

Figure 1. Educational materials used ve the first and the second form used for assessment

A: Educational materials used, B: The first form containing the name table and the answer table, C: The second form containing example of questions on heart anatomy

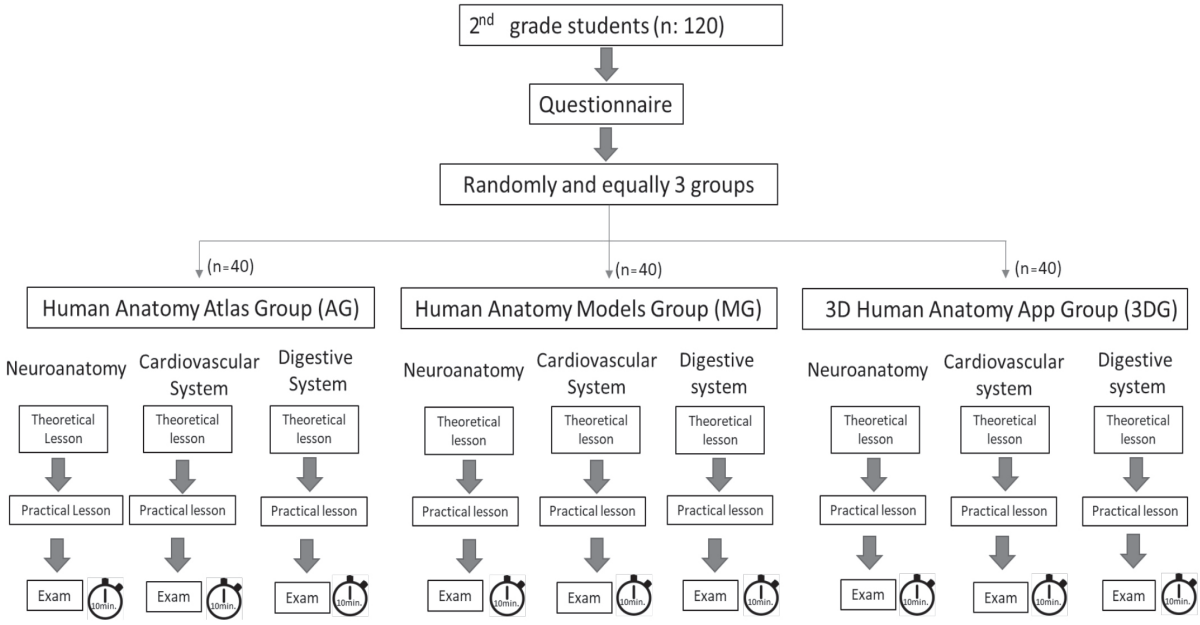

Figure 2. Schematic illustration of the grouping and assessment

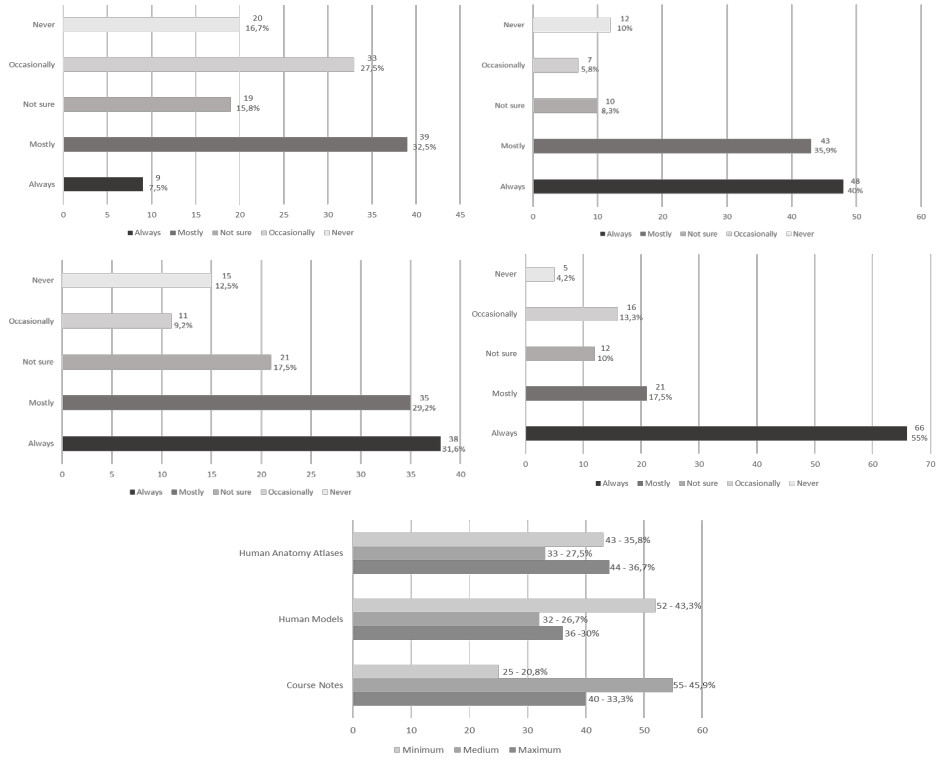

Figure 3. Outcomes of the questionnaire

A: Do you enjoy studying anatomy? B: Do you think it is sufficient to work on a human model in anatomy practical lessons? C: Do you find the duration of anatomy practical lesson sufficient? D: Do you think that learning would be insufficient if cadavers were not used in anatomy practical lessons? E: List the resources you used while studying the anatomy lesson from the most to the least

As a result of the variance analysis in Table 2, statistically significant differences were calculated as F=5.841, F=8.782 and F=6.856 (p<0.05). To test the source of the difference, the Tukey test was used because all of the post-hoc tests showed a homogeneous distribution. For all courses, with 3DG the direction of difference is between both AG and MG. There is no difference between AG and MG. 3DG is more successful in all lessons than other groups.

As a result of the variance analysis in Table 3, there is no statistically significant difference F=0.420, F=1.035 and F=1.293 (p>0.05). The modules we evaluated for the three training groups we formed did not differ significantly in terms of mean success scores

Table 1. Mean, standard deviation, minimum and maximum values of the exam according to modules and groups

Groups	Neuroanatomy		Cardiovascular system		Digestive system	
	Min-max	Mean ± SD	Min-max	Mean ± SD	Min-max	Mean ± SD
AG	56-88	73.5±10.78	52-96	69.5±12.54	52-96	71.4±13.81
MG	52-92	73.6±11.08	52-88	69.6±11.64	52-92	69.8±14.37
3DG	60-100	80.9±11.43	64-100	78.7±9.29	64-100	80.0±11.60

AG: Human Anatomy Atlas group, MG: Human Anatomy Models group, 3DG: 3D Human Anatomy App group, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Distribution showing the comparison of One-Way ANOVA test for practice groups according to modules

Module	Group	N	X	SD	F	P	Direction of the difference
Neuroanatomy	AG	40	73.5	10.78	5.841	0.004	Between 3DG and both MG and AG
	MG	40	73.6	11.08			
	3DG	40	80.9	11.43			
Cardiovascular system	AG	40	69.5	12.54	8.782	0.000	Between 3DG and both MG and AG
	MG	40	69.6	11.64			
	3DG	40	78.7	9.29			
Digestive system	AG	40	71.4	13.81	6.856	0.002	Between 3DG and both MG and AG
	MG	40	69.8	14.37			
	3DG	40	80.0	11.60			

AG: Human Anatomy Atlas group, MG: Human Anatomy Models group, 3DG: 3D Human Anatomy App group

Table 3. Distribution showing the comparison of One-Way ANOVA test for the modules according to the practise groups

Group	Module	N	X	SD	F	p	Direction of the difference
AG	Neuroanatomy	40	73.5	10.78	1.035	0.359	-
	Cardiovascular system	40	69.5	12.54			
	Digestive system	40	71.4	13.81			
MG	Neuroanatomy	40	73.6	11.08	1.293	0.278	-
	Cardiovascular system	40	69.6	11.64			
	Digestive system	40	69.8	14.37			
3DG	Neuroanatomy	40	80.9	11.43	0.420	0.658	-
	Cardiovascular system	40	78.7	9.29			
	Digestive system	40	80.0	11.60			

AG: Human Anatomy Atlas group, MG: Human Anatomy Models group, 3DG: 3D Human Anatomy App group, SD: Standard deviation

among each other. But in all of them, 3DG's mean score was the highest.

Discussion

Although the cadaver is an indispensable educational material that gives students experience by reaching the secrets of the body, its use in education has become difficult due to its serious disadvantages (cost, time-consuming, supply difficulties, etc.). Thus, developing technology with the advantages it provides, has made us question use of it in anatomy education (7,28). In some medical faculties in United States, programs that display the 3D human body in virtual reality to the finest detail, medical images such as ultrasound and computed tomography (CT), and educational models using human models are used (38). While interactive 3D anatomy software in anatomy classes is used at Iowa Carver College of Medicine, (36) The Ohio State University College of Medicine has started to use ultrasound as an innovative strategy in its education curriculum (39). Some authors reported the disadvantages of cadaverless anatomy education such as being difficult for students to develop depth perception in a virtual body, missing the opportunity to see natural anatomical variations of the body. Not working in the human body would create a deficiency in forming a medical identity, and would cause losing the consciousness of encountering with death (4,11,38).

In a study conducted in Canada (40), 93 medical students were divided into two groups. The groups received 15 hours of muscle practice training, the first group on a cadaver already dissected and prepared, the second group by dissecting the cadaver themselves. In the subsequent examination, no difference was noted in terms of success between the groups.

In a study investigating medical students' anatomy education's efficiency in using 3D printed models of skull (41), they concluded that the group of students working using this model was more successful in exams than those using atlas and cadaveric skulls. In a study (42) in which 52 students participated in Monash University, a pre-test including questions on the subject was applied to the students before the cardiovascular system practical training. Later, students were randomly distributed to three groups according to the educational materials, which are cadavers, 3D printing and a combination of the two and were given practical training and a post-test. Post-test scores were found to be significantly higher in the 3D printing group compared to other groups. In the study, the students who use this method emphasized that they had an advantage of particularly the structures being colored compared to cadavers. Curtin University has investigated the use of 3D printing models in anatomy education (43). Twenty-three students were divided into three education groups: 3D printing models, cadavers, and plastinated. An anatomy test and a questionnaire were conducted on the structures studied. 85% of the students reached correct answers for 3D printing models compared to other groups. 74% stated that the most useful method for learning structures is 3D models. They emphasized that three-dimensional printing models have high potential in facilitating anatomy learning.

In the study conducted at Health Sciences at Curtin University (44), Anatomage table, which presents a cadaver in a virtual scale on a table-sized iPad type screen, was used in practical lessons and then students were asked to evaluate. In the questionnaire conducted with the participation of 326 students, 79.5% found it useful in showing the size and neighbourhood of the organs and 56.7% emphasized that the structures could not be understood due to software errors in this method and poor image quality in some regions. Ludwig-Maximillian's University (45) divided the students who had previously studied anatomy into three groups using the Magic Mirror, Anatomage table and radiology atlases to investigate the learning effects provided by different systems. All three groups were evaluated with a pre-test and post-test consisting of multiple-choice questions. While there was an increase in the post-test scores of the groups using Magic Mirror and radiology atlases compared to the pre-test, no increase was observed in the test scores for the Anatomage Table group. Researchers have pointed out that the Magic Mirror system is important for learning compared to built-in anatomy learning tools.

In a study (46), the faculty created the Human Anatomy Education Page on Facebook, the social media site most frequently visited by University of Sharjah students, and researched how they could carry anatomy education beyond traditional methods. This page has been included in the educational resources of medical students for two academic years.

Most students agreed that the page was effective in contributing to learning and that Facebook could be a suitable learning environment. In this way, they stated that the education-oriented Facebook pages will lead many new technological ideas with increasing learning, ease of use, fast accessibility and low cost.

There are some studies stating that the use of ultrasound, a method that allows real-time visualization of anatomical structures and their relationships, has the potential to provide pre-clinical training in physical diagnosis (47). In the study conducted at the University of Pittsburgh School of Medicine, most students stated that this technology is very positive for anatomy education. They stated that although there are problems with the integration of ultrasonography (USG) into anatomy education, these can be easily overcome. Students "willingness to learn and anatomists" desire to teach with USG has led to the widespread application of ultrasound-based teaching initiatives in medical schools around the world (48).

When a survey of the University of Sydney medical school graduates (49) revealed students' dissatisfaction with their anatomy education, medical imaging was integrated into the anatomy curriculum. Three separate ultrasound training courses covering abdominal, pelvic and vascular anatomy were included in the practice of students taking anatomy lessons in three years. When asked for their opinions, more than 90% of the students stated that they were satisfied with their anatomy education with ultrasound, and more than 75% stated that they understood the abdominal anatomy better with ultrasound.

In a study at the University of Melbourne (50), when a transthoracic echocardiography module was added to the anatomy curriculum of medical students, 90% of the students stated that this method made anatomical structures easily visible, 83% stated that it reinforced learning and 83% requested that this method should consistently be used.

Research conducted at The Stanford University Division of Clinical Anatomy (51) found that cadaveric anatomy education's being supported by a wide variety of tools such as photos, videos and 3D models, while simplifying anatomy, actually also involve problems because of limited use and distribution. However, they stated that photogrammetry, used to create digital 3D models, tries to overcome such deficiencies by creating digital models from cadaver samples. In their study, they produced digital 3D models of 8 different regions from cadaver samples using photogrammetry. The faculty lecturers of the Stanford University Department of Clinical Anatomy stated that these models represented the original examples in a real way so their teaching capasity might be much higher. In the study, they emphasized that photogrammetry will have an important place in anatomy education in terms of transforming the cadaver into effective 3D models and providing more visual information compared to many other materials.

In our study, where we evaluated the methods, we used other than cadavers, the students studying by using 3D Human Anatomy Apps were more successful and were satisfied with the contribution of this method which they never used before, in learning and they stated that they would prefer it as a resource. Although the digital education materials used in our studies and in other studies are different from each other, it is seen that they are adopted by the students because they create a sense of reality close to the cadaver and increase the success. Thus, we think that education models developed using technology should be made cheap and easy to use and thus popularized.

The reliability and validity of the questionnaires conducted to evaluate the education offered to students, is high. Objective evaluation of the education received by students at regular intervals allows to increase the quality of the education offered, to eliminate the deficiencies and to develop new methods. Therefore, student feedback is important in order to achieve the targeted goals of anatomy practical education (52,53).

In a study (54) evaluating the views of the students (n=79) about anatomy education, 68.4% of the students stated that working on models in practical lessons was quite effective in learning anatomy and 70.8% of them stated that the time allocated to education on the model was insufficient. In another study (n=176), 92.1% of the students stated that it was necessary to use auxiliary lesson tools other than cadavers in anatomy practical lessons and when asked about the preferences of the students in the use of cadavers and human models, it was seen that 68.1% chose both. In a study in which 34 students participated in a medical school (55), a questionnaire was conducted to evaluate the students' opinions

about their learning by using the mobile augmented reality method in their practical anatomy education. The students emphasized that learning with mobile augmented reality adds a sense of reality, increases the interest in the lesson by embodying the relevant subject and stated that providing a flexible learning environment, it is useful in their individual work and such applications should be expanded. In another study (56), in a survey of 430 students from medical and health sciences, the majority of students found it necessary to include anatomical structures created using 3D printing technology in education. In these studies, it is seen that students adopt more the newly created methods.

In our questionnaire study, 40% of the students stated that they enjoyed studying anatomy, 75.9% of the students stated that it was sufficient to work on the model, 60.8% stated that the practice lesson time was sufficient and 72.5% of them said that learning would be insufficient if cadavers were not used in practical lessons, 36.7% stated that they mostly used the printed human anatomy atlas while studying for the practice lesson. However, it was observed that the students who used the 3D app in our practical training increased their success and so more adopted this method. Evaluating practical training with different materials in all subjects of anatomy will increase the success.

Conclusion

It is essential for students to understand the human body in order to be a well-equipped physician with a holistic approach. For this, practice in medical education is essential. 3D anatomy applications, one of the methods used outside cadaver in recent years, are new to anatomy education in terms of examining the structures from all angles, ending learning anatomy in a static or in-place form like a cadaver, showing the anatomical changes in a living organism functionally and visually increasing the permanence of learning. Offered a point of view. In our study, we found that this method increases the success of students. Nowadays, due to pandemic diseases, the importance of 3D Human Anatomy Apps, which provide a flexible and individual learning environment for remote anatomy practical training, has increased. For this reason, we believe that these educational models developed by using technology should be widely used, developed, cheapened, easily accessible, and should be a part of education life.

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Ethics

Ethics Committee Approval: Ethics committee approval is not required for the study.

Informed Consent: Patient consent is not required.

Peer-review: Externally peer-reviewed.

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