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Review / Derleme

Selexipag: A New Treatment Agent for Pulmonary Arterial Hypertension

Selexipag: Pulmoner Arteriyel Hipertansiyon için Yeni Bir Tedavi Ajanı

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Abstract

Pulmonary arterial hypertension (PAH) is a rare disease which is characterized by the progressive increase of pulmonary arterial pressure. PAH can lead to right cardiac insufficiency and death. Conventional and other treatment modalities that target the physiopathological and etiopathological causes of the disease are currently being used. Selexipag is an oral selective prostacyclin receptor agonist which was developed to overcome the pathophysiological mechanisms that play role in the PAH.

Keywords
Pulmonary arterial hypertension, prostacyclin receptor agonist, novel theraphy

Öz

Pulmoner arteriyel hipertansiyon (PAH); pulmoner vasküler direnç ve arteriyel basınçta progresif artışla karakterize, sağ kalp yetmezliği ve erken ölüme neden olan nadir görülen bir hastalıktır. PAH tedavisi için geleneksel (konvansiyonel), hastalığın fizyopatolojisine yönelik, etiyopatolojiye yönelik ve diğer tedaviler kullanılmaktadır. Selexipag da PAH fizyopatolojisine yönelik geliştirilen güçlü, ağızdan kullanılabilen selektif prostasiklin reseptör agonistidir.

Anahtar Kelimeler
Pulmoner arteriyel hipertansiyon, prostasiklin reseptör agonist, yeni tedavi

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Introduction

Pulmonary hypertension (PH) is defined as having a mean pulmonary artery pressure ≥25 mmHg in the resting right cardiac pressure examination via catheterization. Pulmonary arterial hypertension (PAH) is a general description used in order to define progressive disorders that leads to right ventricular failure due to the increased pulmonary vascular pressure even the pulmonary capillary wedge pressure is in between normal range (1). PAH is a chronic and progressive disease and it is related to mortality and morbidity. The disease is characterized by the increase of pulmonary vascular resistance and this condition leads to overloading and hypertrophy in the right ventricle and early death (2,3). The processes that have been experienced in the search for the mechanisms related to the disease led us to the discovery of the drugs which target the 3 major pathways.

These pathways are prostacyclin, endothelin and nitric oxide pathways (3). Selexipag is a selective, long lasting, non-prostanoid, prostacyclin receptor agonist (4). Other drugs that affect the prostacyclin have a short half-life and they are administered by intravenous, subcutaneous or inhalation in general (5). There are some clinical trials to evaluate oral prostanoid and non-prostanoid IP receptor agonists in the treatment of PAH (Table 1). Selexipag was approved by the food and drug administration in December 2015 for using in the curative process of PH in order to delay the progress of the disease and to decrease the hospitalization risk (Figure 1) (6).

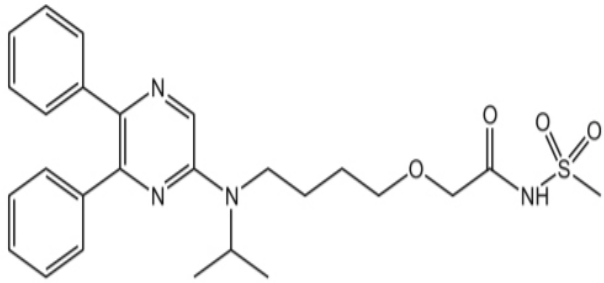

Figure 1. Structure of selexipag (6)

Table 1. Clinical trials examining oral prostanoid and non-prostanoid IP receptor agonists in the treatment of PAH

Trial	Study drug	n	Weeks	Background PAH therapy	Primary endpoint: treatment effect	Secondary endpoints
ALPHABET (12)	Beraprost	130	12	None	6 MWD: 25 meters, p=0.04	Progress in Borg dyspnea index versus placebo; no remarkable alteration in functional class, disease progression or hemodynamics
Beraprost study group (13)	Beraprost	116	52	None	Disease progression: placebo 17% versus beraprost 29%, p=0.254	No noticeable improvement in 12-month peak VO_2, Borg dyspnea index, 6 MWD, WHO functional class or hemodynamics
FREEDOM-C (15)	Treprostinil	350	16	100%	6 MWD: 11 meters, p=0.07	Development in dyspnea fatigue index score; no important difference in clinical deterioration, Borg dyspnea score, functional class
FREEDOM-C2 (16)	Treprostinil	310	16	100%	6 MWD: 10 meters, p=0.09	No remarkable chance in clinical deterioration, functional class, Borg dyspnea score, NT-proBNP, CAMPHOR
FREEDOM-M (17)	Treprostinil	349	12	None	6 MWD: 26 meters, p=0.01	No remarkable chance in Borg dyspnea score, functional class or symptoms of PAH
Selexipag phase 2 study (28)	Selexipag	43	17	100%	ΔPVR: -30%, p<0.01	Improvement in cardiac index; no remarkable chance in 6 MWD, Borg dyspnea score, NT-proBNP
GRIPHON (29)	Selexipag	1.156	64-71	80%	Disease progression: HR 0.6, p<0.001	Betterment in 6 MWD (12 meters, p<0.01) and NT-proBNP, no significant observation in proportion with worsening functional class

MWD: Minute walk distance, VO_2: Peak oxygen consumption, WHO: World Health Organization, NT-proBNP: N-terminal probrain natriuretic peptide, CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review, PAH: Pulmonary arterial hypertension, PVR: Pulmonary vascular resistance, HR: Hazard ratio

Pharmacodynamics

IP receptor is one of the 5 prostanoid receptors. Prostacyclin induces the vasodilatation by activating IP receptor and inhibits the proliferation of vascular smooth muscles (6). It also has antithrombotic and anti-inflammatory effects (7,8). Selexipag acts similar to the endogenous PGI2. However; it is a non-prostanoid IP receptor agonist, not an analogue of PGI2 (5). Selexipag is more selective in terms of IP receptors compared to other prostanoid receptors, unlike prostacyclin analogues. This selectivity seen in selexipag against the IP receptors can minimalize the side effects derived from stimulation of other prostanoid receptors, thus increasing the tolerability of the selexipag. Several PGI2 analogues show a weak selectivity against IP receptors since they have a high affinity against prostaglandin E (EP) receptors. Selexipag is well tolerated and the gastrointestinal side effects are minimal since these side effects such as vomiting are related to the stimulation of EP-3 (9). Furthermore; side effects of the prostacyclin analogues are often related to the changes in the plasma levels of the drug. Since selexipag is hydrolyzed to its active metabolite in liver rapidly; the peak-through fluctuations of the active metabolite, thus the risk of side effects are decreased. Although selexipag and the active metabolite act like endogenous prostacyclins, they are different from the prostacyclins pharmacologically (10). Selexipag is hydrolyzed to its active metabolite (ACT-333679) via carboxylesterase 1. The active metabolite is 37 times more potent than the selexipag. ACT-333679 has 130 times higher affinity against the IP receptors compared to the prostacyclin receptors (6,11,12). Prolonged exposure of *in vitro* IP receptors with the PGI analogues (iloprost, beraprost and treprostinil) results in severe desensitization of these receptors (13-15). Therefore the dose needs to be increased in the treatment of PAH with PGI2 infusion. ACT-333679 does not result in desensitization or internalization of IP receptors. Consistent vasodilatation induced by the selexipag exposure does not decrease after the repeated doses. This finding indicates that selexipag is not related with severe IP receptor desensitization. Therefore it can be asserted that increasing the dose is less likely necessary in order to maintain the efficacy (16).

It was demonstrated that selexipag and the active metabolite inhibits the platelet aggregation dose-dependently (IC50 of 5.5 μM and 0.21 μM, respectively). However, any effect on the platelet aggregation wasn't seen with the dose range between 400-1800 mcg/2 times a day (6). Safety and efficacy of the selexipag were assessed in a proof-of-concept study conducted on PAH patients. The patients (class 2-3 according to the World Health Organization functional classification) that had been treating with fixed dose of endothelin receptor antagonist and/or phosphodiesterase type (PDE)-5 inhibitor were divided into 2 groups as selexipag and placebo users. The drug dose was increased to the maximum dose of 800 μg twice a day from the initial dose of 200 μg twice a day gradually. The study revealed that geometrical mean value of the pulmonary vascular pressure 30.3% decreased at the end of 17 weeks treatment [95% confidence interval (CI) -44.7 to -12.2%; p=0.0045]. Cardiac index was found as 0.41 L/min/m^2 (95% 0.10-0.71) increased in patients receiving selexipag. Selexipag was considered as safe in terms of the pharmacological effects and well tolerated (4). Selexipag didn't cause QT prolongation at the maximum dose of 1600 μg twice a day in healthy volunteers (11,17). In another study conducted on healthy volunteers assessing the interaction of selexipag and warfarin it was stated that selexipag didn't affect the pharmacodynamic effects of warfarin on international normalization ratio (11,18).

Pharmacokinetics

The pharmacokinetics of selexipag and its active metabolite are not affected by the severity of the disease and do not change in time. Selexipag and its active metabolite reach their maximum plasma concentration in 1-3 hours and 3-4 hours after taking orally, respectively (11). In a study of Kauffman et al. (19) it was stated that selexipag and its active metabolite reached their maximum plasma concentration in 2.5 and 4 hours respectively. In the same study; the mean half-life of selexipag and ACT-333679 were found in between 0.7-2.3 hours and 9.4-14.22 hours, respectively (6,19,20). Maximum bioavailability of selexipag is 49% in humans. This can be derived from the first-pass effect of selexipag (11). In preclinical studies conducted on monkeys, rats and dogs ACT-33679 were showed to have a high bioavailability (102% in rats and 80% in dogs). In the same study; it was also showed that ACT-333679 has a long half-life (3.6 hours in rats, 6.2 hours in dogs)

(21). The plasma near peak level of the ACT-333679 was found as more than 8 hours.

Oral use of selexipag concomitant with foods delays the absorption of selexipag causing a delay in the peak concentration and 30% decrease in the peak plasma concentration. It was indicated that concomitant use of selexipag with foods can result in a decrease of selexipag absorption and Cmax, delay in median Tmax levels compared to fasted state. It was also stated that exposure of selexipag wasn't affected by the presence of foods whereas exposure of its active metabolite was reduced by 27%. More adverse effects were reported in the fed state compared to fasted state (45% and 17% respectively). This shows that selexipag can be tolerated better when it is used with foods (11). Both selexipag and its active metabolite bind to plasma proteins after they are absorbed. Selexipag is converted to its active metabolite by hepatic carboxylesterase 1. The oxidative metabolism is catalyzed by CYP3A4 and CYP2C8 resulting in the production of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 play role in glucuronidation of the active metabolite (6,11). The half-life of the selexipag is 0.8-2.5 hours and mean clearance is 35 L/h. The terminal half-life of the ACT-333679 is in between 6.2-13.5 hours allowing to be able to use twice a day (6). In a study of Kuwano et al. (16) about the single dose use of selexipag; half-life of the ACT-333679 was found as 7.9 hours. The drug is excreted mainly in feces and urine in a smaller amount. In a study conducted on healthy volunteers, fecal and urinary excretion of radioactive drug material were found as 93% and 12% respectively; However both the selexipag and ACT-333679 were not found in the urine (11). Metabolism of the selexipag and ACT-333679 are not affected by age, gender, ethnicity and weight. Dose adjustment is not necessary in patients with a glomerular filtration rate (GFR) above 15mL/min/1.73 m^2. Any clinical data exists about the dose of the drug in patients having a GFR value below this level. There is no need for dose adjustment in patients with mild hepatic insufficiency whereas decreasing the drug dose from twice a day to once in a day is recommended in patients with moderate hepatic insufficiency. There is not any clinical data about the use of the drug in patients with severe hepatic insufficiency and it is not recommended to use (6,11).

Clinical Studies About the Selexipag

A randomized, double-blind, multi-national, multi-centered, phase-2, proof-of-concept study was conducted by Simonneau et al. (4) in 2012 (NCT 00993408). This study was assessing the efficacy and safety of the selexipag in patients with PAH. In the study of Simonneau et al. (4), selexipag and placebo were randomized in the proportion of 3:1 in 43 adult patients with PAH. The etiology of the PAH in the aforementioned study includes idiopathic PAH, PAH-related connective tissue disorder, hereditary PAH, corrected congenital heart disease or anorexigen use related PAH. Patients had been using ERA and/or PDE-5 inhibitor during at least 12 weeks at a fixed dose. Selexipag dose had been increased from the initial dose of 200 µg twice daily to maximum tolerable dose of 800 µg twice daily in 35 days. Right cardiac catheterization had been performed at both the initiation and the end of the treatment. The geometric mean level pulmonary vascular pressure had been found as 30.3% decreased in selexipag group compared to placebo group at the end of 17 weeks of treatment (95% CI -44.7 to -12.2%; p=0.0045). The cardiac index had also been found as significantly increased (0.41 L/min/m^2, 95% 0.10-0.71) in selexipag group. Selexipag was considered as safe in terms of pharmacological effects and well tolerated (4).

GRIPHON study is a multi-national, multi-centered, double-blind, placebo-controlled phase-2 study (NCT01106014) and it investigates the efficacy and safety of the oral use of selexipag. It is the longest study that has been conducting about PAH. The study consists patients from 181 medical centers located in 39 countries located in North and Latin America, Europa, Pacific Asia and Africa. Patient admission was closed in May 2013 with the final population of 1156 patients. The results of the study were reported as the biggest randomized controlled study conducted on patients with PAH. 80% of the patients had been receiving ERA, PDE-5 or a combination of these two medications for the treatment of PAH. Patients were started on selexipag treatment with the initial dose of 200 µg twice daily and the dose was gradually increased to 1600 µg twice daily. Duration of the treatment was 70.7 and 60.7 weeks for selexipag and placebo, respectively. This important, event focused study was designed in order to assess if the first morbidity development or mortality is delayed or not

with the use of selexipag compared to placebo and to investigate the safety of selexipag. All the morbidity or mortality events reported by the investigators were evaluated by independent and blind critical event committee (22). A total of 1156 patients were treated in this global, long-term phase-3 study for 4.2 years. Development of morbidity or mortality (whichever takes place first) was found as 40% decreased in patients using selexipag compared to placebo (hazard ratio 0.60; 99% CI 0.46-0.78; p/0.001) (Figure 2). In GRIPHON study, general tolerability profile of selexipag was in accordance with prostacyclin

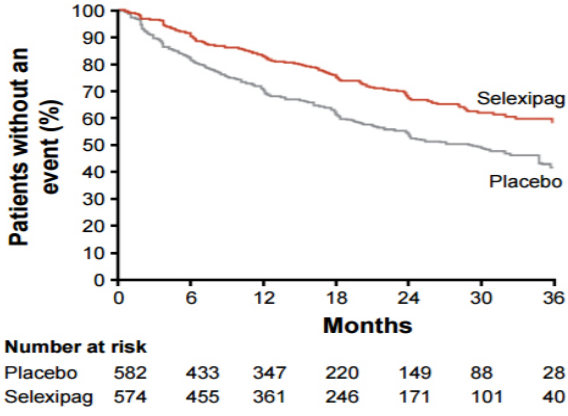

Figure 2. The effect of selexipag on mortality and morbidity in pulmonary arterial hypertension patients according to placebo (GRIPHON study) (2)

Table 2. Adverse events noticed during the GRIPHON clinical trial (2)

Adverse events	Placebo (n=577) (%)	Selexipag (n=575) (%)	p
Headache	189 (33	375 (65)	<0.001
Nausea	107 (19)	193 (34)	<0.001
Diarrhea	110 (19)	244 (42)	<0.001
Pain in jaw	36 (6)	148 (26)	<0.001
Vomiting	49 (9)	104 (18)	<0.001
Pain in extremit	46 (8)	97 (17)	<0.001
Dyspnea	121 (21)	92 (16)	0.03
Worsening of PAH	206 (36)	126 (22)	<0.001
Myalgia	34 (6)	92 (16)	<0.001
Peripheral edema	104 (18)	80 (14)	0.06
Dizziness	85 (15)	86 (15)	0.96

PAH: Pulmonary arterial hypertension

treatments. The length of 6 minutes of walking test was increased in patients using selexipag at the end of 26 weeks, whereas 9 minutes of walking test was found as decreased in patients using placebo (effect of the treatment, 12.0 m; 99% CI 1-24; p=0.003) (22).

Clinical Use and Adverse Effects

Recommended initial dose is 200 µg twice daily and the dose can be increased week by week up to the maximum tolerable dose of 1600 µg twice daily and the maintenance dose is decided based on tolerability. The initial dose is also 200 µg in patients with mild hepatic insufficiency and it can be increased 200 µg week by week based on the tolerability. There is no data about the dosing of selexipag in patients with severe hepatic insufficiency and it is not recommended to use. Dose adjustment is not necessary in patients with a GFR above 15 mL/min/1.73 m^2. Any clinical data exists about the dose of the drug in patients having a GFR value below this level (6,11). Selexipag was well tolerated in patients with PAH in the GRIPHON study. The adverse effects were similar with other prostacyclin analogues and these adverse effects were encountered during the dose titration, mostly. Incidence of serious adverse effects ≥1 were similar in placebo and selexipag group (47.1% and 43.8%, p=0.26 respectively). Headache, diarrhea, nausea, vomiting, mandibular pain, pain in the extremities, myalgia and flushing adverse effects were more common in selexipag group (Table 2). The ratios of patients who left the treatment due to the adverse effects were 14.3% and 7.1% in selexipag and placebo groups, respectively. The most common adverse effects that led the patients to left the treatment were headache (3.3%), diarrhea (2.3%) and nausea (1.7%). Hyperthyroidism was developed in 8 patients in patients on selexipag treatment and 1 patient left the treatment due to this reason (22). The risk of some catheter-related adverse effects that can be seen with the use of Prostaglandin analogues, such as embolism, thrombosis, infection and fluctuations in the received drug dose are decreased in selexipag since it is used orally. Therefore the safety and tolerability profile of the drug is better.

Conclusion

Selexipag is a long-lasting, selective, non-prostanoid oral prostacyclin receptor agonist. High

selectivity of the selexipag against IP receptors decreases the rate of adverse effects and helps the drug to be well tolerated. It is enough to use it since the half-life of its active metabolite is 7.9 hours. It can be asserted that selexipag is a good alternative of current prostacyclin analogues based on these superiorities. It is a promising candidate for oral combination treatment in PAH patients using the drugs that affect the major pathways.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Y., H.G., Concept: O.Y., Design: O.Y., H.G., Data Collection or Processing: O.Y., H.G., Analysis or Interpretation: O.Y., Literature Search: O.Y., H.G., Writing: O.Y.

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Original Article / Özgün Araştırma

Micro-shear Bond Strength of Aged Resin Composite Repaired with Different Universal Adhesives

Farklı Üniversal Adezivlerle Tamir Edilen Yaşlandırılmış Kompozit Rezinin Mikro-Makaslama Bağlanma Dayanımı

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Abstract

Objective: This study evaluated the effect of two different universal adhesives on the repair bond strength of aged resin composite.

Materials and Methods: Forty-four composite resin disks were prepared (5 mm x 3 mm). The composite disks randomly assigned into four groups after aging. Specimens were repaired with resin composite using four different repair procedure; Porcelain primer + Clearfil S3 Bond Plus, Single Bond Universal, Clearfil Universal Bond, Clearfil S3 Bond Plus, then they were subjected to micro-shear bond strength testing. Data were analyzed using ANOVA and Tukey's HSD ($p<0.05$).

Results: Additional silane treatment significantly affected the repair bond strengths ($p<0.05$). No statistical difference was found in repaired groups with universal adhesives. One-step self-etch adhesive showed lower bond repair strength values in aged composite repair ($p<0.05$).

Conclusion: Repair of composite restorations with universal adhesives cannot suggest without additional silane application.

Öz

Amaç: Bu çalışma iki farklı üniversal adeziv sistemin yaşlandırılmış rezin kompozitlerin tamir bağlanma dayanımı üzerindeki etkileri incelemektedir.

Gereç ve Yöntemler: Kırk dört adet kompozit disk hazırlanmıştır (5 mm x 3 mm). Kompozit disklerin yaşlandırılmasının ardından (ısıl-döngü 10.000), rastgele dört gruba ayrılmıştır. Örnekler rezin kompozit ile dört farklı tamir prosedürü izlenerek tamir edilmiştir: Porselen primer + Clearfil S3 Bond Plus, Single Bond Universal, Clearfil Universal Bond, Clearfil S3 Bond Plus, ardından mikro-makaslama bağlanma dayanımı testi uygulanmıştır. Veriler ANOVA ve Tukey's HSD kullanılarak analiz edilmişlerdir ($p<0,05$).

Bulgular: İlave silan uygulanması tamir bağlanma dayanımını önemli ölçüde etkilemiştir ($p<0,05$). Üniversal adezivler ile tamir edilen gruplar arasında istatistiksel olarak anlamı bir fark yoktur. Tek-basamaklı kendinden asitli adeziv diğer gruplardan daha düşük tamir dayanımı göstermiştir.

Sonuç: Üniversal adezivlerin, ilave silan uygulaması olmaksızın tek başına kompozit rezinlerin tamirinde kullanılması önerilmez.

Introduction

Following the improvements in the bonding systems, curing systems and enhanced mechanical and physical properties of the resin systems, composite resin restorations have become routine in restorative dentistry. However, similar to other restorative materials, composite resin restorations have limited longevity (1). Failed restorations are generally totally replaced and results in considerable amount of tooth structure loss (2). Consistent with "minimum intervention" dentistry philosophy, it is suggested that the defective restorations should first be evaluated for the repair options rather than total replacement (3).

In general, bonding between two composite layers is achieved in the presence of an oxygen inhibited layer of unpolymerized resin (4). Aged composite restorations do not contain unpolymerized surface layer. In order to successfully repair such aged composite restorations, a strong bond should be create between the old composite restoration and the new repair material.

Mechanical retention can be created with several methods. These methods include creating retention holes and undercuts, roughening the surface with diamond burs, applying phosphoric or hydrofluoric acid to the surface and applying air abrasion with silica coated alumina particles.

In addition, chemical bond between aged composite and repair material may be achieved by applying special primers as silane coupling agents (5-8).

Currently repair systems with various conditioning protocols and adhesive systems are commercially available. "Universal adhesives" are simplified systems, usually containing all bonding components in a single bottle (9-11). They can be applied either in etch-and-rinse or self-etching bonding protocols according to manufacturer's instructions. Some universal adhesives may contain silane in their composition and eliminates the silanization step when bonding to glass ceramics, hybrid materials and resin composites.

The studies investigating the (12-14) different repair systems and protocols are available; however, there is lack of information regarding the use of universal adhesives to repair the aged composite restorations. Therefore, the aim of this study is to investigate the micro-shear bond strength (μSBS) of different universal adhesive systems applied on aged composite resins.

Materials and Methods

Specimen Preparation

Forty-four resin composite disc shape sample (5 mm diameter, 3 mm height) were prepared in a custom-made stainless steel mold with a resin composite (Clearfil Majesty Esthetic, Kuraray, Osaka, Japan). Each increment was cured for 20 s with a light emitting diode curing unit (SDI Radii Plus, SDI Limited, Australia). Light intensity was assured to be higher than 1000 mW/cm^2 (Hilux Ledmax curing lightmeter Benlioglu Dental, Turkey).

To create a uniform surface, top surfaces of the samples were abraded with 600 grit silicon carbide papers (P1000-P4000Metkon, Gripo 2v Grinder-Polisher, Turkey). All discs were cleaned in ultrasonic cleaner. Cleaned specimens were kept in distilled water at 37 °C for 24 h. All specimens were aged for 10.000 cycles, between 5 and 55 °C, dwell time 30 s, transfer time 10 s (Thermocycler THE-1100, SD Mechatronik, Feldkirchen-Westerham, Germany). Then, each top surface of the samples roughened with a new diamond bur (150 μm grit size). Diamond burs was used with five back and forth strokes for a total of 10 s using a high-speed hand-piece under water-cooling. Samples were cleaned with water and air-dried. Subsequently, forty-four samples of each composite material were randomly assigned into four groups for surface treatments (n=11).

Group 1: Phosphoric acid gel (35%) + Porcelain primer + Clearfil S3 Bond Plus (positive control)

Group 2: Phosphoric acid gel (35%) + single bond universal

Group 3: Phosphoric acid gel (35%) + Clearfil Universal Bond

Group 4: Phosphoric acid gel (35%) + Clearfil S3 Bond Plus

Materials used in the study are shown in Table 1 and the application steps are presented in Figure 1.

For the repair procedure, polyethylene tube (1.5 mm length, 0.8 mm internal diameter, (Unomedical, ConvaTec Limited, UK) was placed on the bonding area. Then, the same composite used in the preparation of discs, was packed into tube and cured for 20 s. Thereafter, all samples were subjected to additional thermal cycling procedure as previously described.

Table 1. Adhesive compositions and application procedures, as described in safety data sheets and instructions

Brand	Material type	Chemical composition	Application	Manufacturer
Single Bond Universal	Muti-mode universal adhesive	MDP phosphate monomer, Dimethacrylate resins, HEMA, vitrebond™ copolymer, filler, ethanol, water, initiators, silane	Applied the one coat adhesive with disposable applicator to the entire sample surface, rub it in for 20 s and air dried the solvent with an air syringe 5 sec. Light cured 10 s	3 M ESPE, St. Paul, USA
Clearfil Universal Bond	Muti-mode universal adhesive	10 MDP, Bis-GMA, HEMA, ethanol, hydrophilic aliphatic dimethacrylate, colloidal silica, camphorquinone, silane coupling agent, accelerators, initiators, water	Applied the one coat adhesive with disposable applicator to the entire sample surface, rub it in for 10 s and air dried the solvent with an air syringe 5 sec. Light cured 10 s	Kuraray, Okayama, Japan
Clearfil S3 Bond Plus	One-step self-etch adhesive	MDP, HEMA, Bis-GMA, hydrophilic aliphatic dimethacrylate, hydrophobic aliphatic methacrylate, colloidal silica, dL-camphorquinone, accelerators, initiators, water	Applied the one coat adhesive with disposable applicator to the entire sample surface, leaved in place for 10 s. Air dried the solvent with an air syringe 10 s. Light cure for 10 s	Kuraray, Okayama, Japan
Porcelain primer		Silane with ethanol and acetone	Applied the one coat porclain primer with disposable applicator to the entire sample surface, allow to dwell for 30 seconds and air dried the solvent with an air syringe	Bisco Inc., Shaumburg, IL, USA
Clerarfil majesty esthetic	Nano-hibrit composite	Bis-GMA, hydrophobic aromatic dimethacrylate, hydrophobic aliphatic methacrylate, silanated barium glass filler, pre-polymerized organic filler, dL-camphorquinone, initiators, accelerators, pigments	Placed the A2 shade product into the stainless steel mold as two increments, and each intrement cured for 20 s	Kuraray, Okayama, Japan
K-etchant gel		Phosphoric acid, water, colloidal silica, dye	Applied it to the entire sample surface for 60 s. Washed thoroughly and dried with an air syringe	Kuraray, Okayama, Japan

HEMA: Hydroxyethyl methacrylate, MDP: Methacryloyloxydecyl dihydrogen phosphate, Bis-GMA: Bisphenol A-glycidyl methacrylate

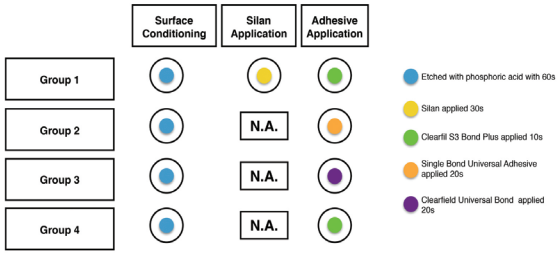

Figure 1. Application steps of repairing aged composite

The polyethylene tube was removed using a scalpel blade and each samples was surveyed with stereomicroscope to verify that no bonding defects, air bubble inclusions, or interfacial gaps were present.

Micro-Shear Bond Strengths (μSBS) and Failure Analysis

Bond strength was tested with a universal testing machine (Z010, Zwick, Ulm, Germany). A shear force was applied to the adhesive interface through a chisel-shaped loading device at a crosshead speed of 1 mm/min. Load at debonding was recorded, and μSBS σ

was calculated using the load at failure F (N) and the adhesive area A (mm^2): $\sigma=F/A$.

The debonded area was inspected for failure mode analysis with a stereomicroscope at 25× magnification (M3Z, Leica Microsystems, Wetzlar, Germany).

The failure mode was classified as, cohesive in aged composite, adhesive at interface, cohesive in new composite (including failures within the adhesive layer and/or composite), mixed adhesive-cohesive.

One-way analysis of variance (ANOVA) and post hoc Tukey's multiple comparisons were used to determine statistical differences in μSBS within groups at a significance level of 0.05.

Results

The results of the μSBS test are presented in Figure 2. Positive control group (Porcelain primer + Clearfil S3 Bond Plus) showed highest repair strength values and there is significant difference compared to the other groups ($p<0.05$). Single Bond Universal and Clearfil Universal Bond groups showed similar bond strength values ($p>0.05$). Clearfil S3 Bond Plus showed lowest repair strength values and there is significant difference compared to the other groups ($p<0.05$).

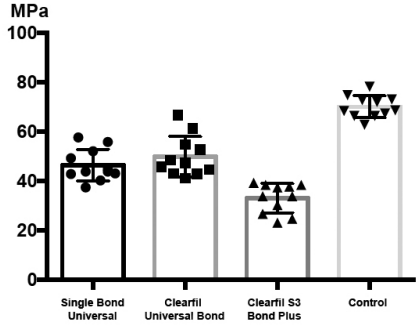

Figure 2. Micro-shear bond strength (MPa: Mega Pascal) of tested adhesives

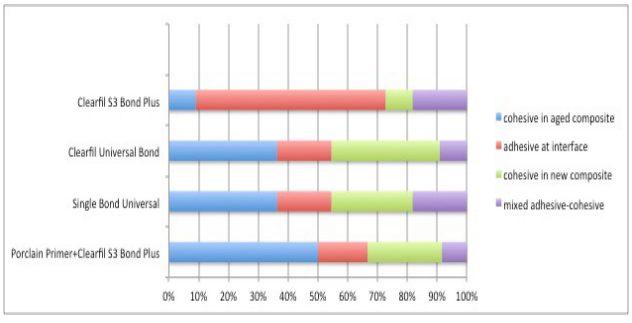

Figure 3. Failure mode (%) for all groups of the composite specimens

Failure Mode

For positive control group most failures were "cohesive" in aged and new composite (81.8%) and only a few fractures as "adhesive interface". On the contrary, in Clearfil S3 Bond Plus group most failures were adhesive interface (63.6%). For universal adhesive groups (Single Bond Universal and Clearfil Universal Bond), similar to the positive control group, most failures were "cohesive" in aged and new composite (resp. 63.6% and 72.7%) (Figure 3). No voids or porosities in the interface were detected.

Discussion

Repairing old composite restorations would be considered as a less invasive and cost-effective treatment approach to extend the service period of aged composite.

A great number of surface conditioning methods and adhesion promoters have been introduced to increase the repair strength of composites, such as roughening with burs, acid etching with hydrofluoric or phosphoric acid, air-borne particle abrasion with aluminium oxide with or without silane coupling agents and resin based adhesive systems (8,15-18). Nevertheless, there is still no universal repair technique recommended for repairing the aged composite restorations (7).

Generally phosphoric or hydrofluoric acids are used as a conditioning agent for substrates. Phosphoric acid is effective on enamel and dentin but has no direct effect on surface characteristics of restorative materials (6). Moreover, studies have shown that phosphoric acid is not capable of increasing the micro-retentiveness of the surface (19,20). However, some studies revealed that phosphoric acid treated specimens have higher repair bond strength compared to the negative control (7,16).

Using hydrofluoric acid as a conditioning agent is another approach for repairing old composite restorations. Hydrofluoric acid dissolves glass particles in most of the composites resins but does not affect the resin matrix. Nevertheless, the effect of hydrofluoric acid is influenced by the composition of the filler particles in the composite material. For example, the effect of hydrofluoric acid on zirconium fillers is less than barium-glass fillers (6). Furthermore,

several studies demonstrated that hydrofluoric acid have no effect in repairing composite restorations. (21-23). In addition, phosphoric acid etching is much safer than hydrofluoric acid for clinical use in patient mouth (24-26).

Following surface conditioning, chemical adhesion might be create using special primers (27). For this purpose, the most preferred material is a silane coupling agent which can function as mediators and promote adhesion between dissimilar, inorganic and organic, matrices through dual reactivity (28). Two types of Silanes are used in the dentistry; hydrolyzed and non-hydrolysed. The hydrolyzed silanes are ready-to-use materials and they applied as a separate step in the bonding procedure. The nonhydrolized silanes must be activated with acid before use, therefore, depending on the adhesive system used, they are mixed with primer or adhesive (6). Researchers reported that the use of silane coupling agents significantly increased the bond strength of repaired composite resins (18,27).

Repairing composite resins with phosphoric acid, followed by a silane application, probably combines best effectiveness with safety and seems to be the most feasible for dentists to use (7). Therefore, in this study the additional silan application was used as the positive control group for composite repair.

Recent trend in adhesive dentistry is to simplify bonding procedures by reducing the application steps (29). Universal adhesives contain many ingredients, such as bisphenol A glycidyl methacrylate, hydroxyethyl methacrylate, 10-methacryloyloxydecyl dihydrogen phosphate, and/or silane. The manufacturer of universal adhesives claims that containing silane improved bonding to glass ceramics or resin composites without additional priming procedures.

According to the results of this study the repair strength is significantly higher when a separate step of silane is applied ($p<0.05$). The application of silane-containing universal adhesives alone was as not effective as the tested silane and adhesive combination ($p<0.05$). However there is no significant difference between tested universal adhesives ($p>0.05$).

Repairing old composite restoration is a minimally invasive approach that protects sound tooth structure and increases the longevity of restorations. However, chemical bonding between the repair composite and aged composite must be maximized to ensure an effective repair. According to the results of the study, in order to increase the restoration strength it is suggested to apply an additional silane step during the repair of composite restorations with universal adhesives. Further investigations with different composites, adhesive systems, and surface treatments should be conducted to improve this technique and provide awareness of this treatment option among dentists.

Ethics

Ethics Committee Approval: This study is a laboratory study. No human or animal origin tissue or organ was used in any part of the study. Therefore, it does not require ethical approval.

Informed Consent: This study is a laboratory study. No human or animal origin tissue or organ was used in any part of the study. Therefore, patient consent is not required.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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Original Article / Özgün Araştırma

Antimicrobial Efficacy of Chlorhexidine and Licorice Mouthwashes in Children

Çocuklarda Meyan Kökü ve Klorheksidin İçerikli Gargaraların Antimikrobiyal Etkinliğinin Değerlendirilmesi

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Abstract

Objective: The aim of this *in vivo* study is to evaluate the effectiveness of a simple herbal caries-prevention protocol for reducing salivary *Streptococcus mutans* levels in children.

Materials and Methods: A total of 90 individuals were recruited randomly divided into three groups (n=30). Mouthwashes including chlorhexidine (CHX), licorice and saline were used as tested antimicrobial agents, and saliva samples were collected before rinsing, at the end of 5 min (T1) and 60 min (T2) following rinsing, and the differences were calculated within 5-60 min (T3). Plaques were evaluated following incubation, and counts of the growing colonies were performed in colony forming units (CFU)/mL. Decreases in CFU were calculated in ratio for statistical analysis. Data were analyzed with Kruskal-Wallis, Mann-Whitney U, Friedman and Wilcoxon signed rank tests by Bonferroni correction, using a 0.05 of significance level.

Results: CHX caused significantly different decreases for T1 and T2 ($p<0.05$), but, there were no significant differences between CHX and licorice for T3 ($p>0.05$).

Conclusion: Licorice might be a useful agent for dental procedures and further studies are needed to learn more about the dose of licorice, the ratio of glycyrrhizin and the duration of dental therapy.

Keywords
Licorice, mouthwash, chlorhexidine, children, antibacterial

Anahtar Kelimeler
Meyan Kökü, gargara, klorheksidin, çocuk, antibakteriyel

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Öz

Amaç: Bu *in vivo* çalışmanın amacı, çocuklarda tükürük *Streptococcus mutans* (SM) düzeylerini azaltmaya yönelik basit bir bitkisel çürük önleme protokolünün etkinliğini değerlendirmektir.

Gereç ve Yöntemler: Yapılan bu çalışmada Klorheksidin (CHX), meyan kökü ve serum fizyolojik kullanılmıştır. Toplam 90 hasta, her bir grup için 30 kişi olacak şekilde rastgele 3 gruba ayrıldı. Gargara öncesi, gargaradan 5 dk sonra ve gargaradan 1 saat sonrasında tükürük örnekleri toplanmıştır. Değerlendirmeler gargara sonrası 5 dk (T1), 1 saat sonra (T2) ve aradaki farklılıkları tespit amacıyla 5-60 dk (T3) olarak hesaplanmıştır. Ekimi yapılan örneklerin enkübasyon süresi sonunda plaklar değerlendirmeye alınarak üreyen kolonilerin colony forming Unit/mL (CFU mL-1) olarak sayımları yapılmıştır. CFU değerlerindeki azalmalar istatistiksel olarak analiz edildi. Elde edilen verilerin değerlendirilmesinde Kruskall-Wallis, Mann-Whitney U and Bonferroni düzeltmeli Friedman, Wilcoxon işaret ve testleri ile yapıldı ve yanılma düzeyi 0,05 olarak alındı.

Bulgular: CHX, T1 ve T2 zamanları içerisinde istatistiksel olarak anlamlı düşüşler gösterirken ($p<0,05$), T3 grubunda CHX ve meyan kökü grubunda istatistiksel olarak anlamlı bir farklılık görülmedi ($p>0,05$).

Sonuç: Meyan kökü dental işlemlerde kullanılabilecek yararlı bir ajan olabilir ve meyan kökü oranının, içerisindeki glisirizik asit yüzdesinin ve tedavinin süresi ile ilgili daha ileri çalışmaların yapılması gerekmektedir.

Introduction

Dental caries is a multifactorial, infectious and most common disease, caused by a specific group of cariogenic bacteria (1,2). World Health Organization estimated that 5 billion people of the world's 6.5 billion population are affected by dental caries (3). Dental caries has been prevalent and costly disease in Turkey as well, particularly during childhood. In 2004, caries prevalence was 69.8% (4) and in 2011, it was 46.9% in Turkey (5). Clinical studies indicated that oral colonization of *Streptococcus mutans* (SM) promotes dental caries development in humans (6,7). SM plays an important role in the dental caries by acid production. SM show adherence in retentive areas of the tooth structure, especially pit and fissures (7). In the presence of sucrose, SM efficiently enhance biofilm biomass and promote ecological shifts that lead to emergence of acidogenic and aciduric organisms (8).

People can avoid from dental caries with regular tooth brushing, favorable dietary habits and regular dental check-up (9). Tooth brushing and flossing might be effective to prevent caries. However, in some instances mechanical methods need to be combined with chemoprophylactic agents to prevent tooth caries (10). Various antibacterial agents have been produced and tested to decrease the number of cariogenic bacteria, to reduce acid production and to prevent biofilm formation (2). One such successful chemotherapeutic agent is chlorhexidine (CHX). CHX has antimicrobial activity against SM and also demonstrates antiplaque and antigingivitis properties (11,12). On the other hand, the use of CHX has some side effects such as staining, altered taste sensation, vomiting, increased risk of caries due to fermentation and alcohol content, development of resistant bacterial strains or oral cancers (13,14).

Innovations and recent research in dentistry witnessed a new herbal material named licorice. Glycyrrhiza glabra, known as Licorice root, is one such medicinal plant that has been used since ancient times to relieve coughs, sore throats, gastric inflammation as a traditional herbal remedy (15). It has been used as a sweetener in food and drug industry and Food and Drug Administration listed licorice in generally regarded as safe (1).

Licorice root compounds with their anti-adherence, antimicrobial and anti-inflammatory effects may help treating oral diseases including tooth decay (16,17). Licorice is 50 times sweeter than sucrose and acting as a gustatory stimulus, it can increase salivary flow thus they can provide an anti-caries effect (18).

In recent years, a few studies regarding anti-cariogenic properties of Glycyrrhiza glabra has been published. Chaiya et al. (19) have demonstrated that Glycyrrhiza glabrahas inhibited the growth of SM as well as the adherence ability of the bacteria**.** Jain et al. (15) have showed antimicrobial and cariostatic efficacy of liquorice extracts and recommend that liquorice can be used as a preventive regimen in pediatric dental practice. Hu et al. (20) and Peters et al. (1) have demonstrated that licorice containing lollipop led to reduction in salivary SM in their studies.

The purpose of this *in vivo* study was to evaluate the effectiveness of a simple herbal caries-prevention protocol aimed at reducing salivary SM levels in children.

Materials and Methods

Ethical approval for this study was obtained from the Cumhuriyet University Clinical Research Ethic Committee (2014-02/15) and the study was conducted at the Cumhuriyet University Faculty of Dentistry, Department of Pediatric Dentistry, Sivas, Turkey.

Sample Distribution

In this study, with an α=0.05, β=0.20 and (1-β)=0.90, a total of 90 individuals [48 girls (53.3%, 42 boys (46.7%)] were included in this study and the power of the test was p=0.8099.

Licorice Root Extract Solution Preparation

Two hundred mg of licorice was weighed and mixed with a 20 m of a solution composed of a mixture of distilled water and ethyl alcohol at a rate of 70:30 at 60 °C for 25 minutes. The mixed solution was centrifuged at 3000 rpm for 10 minutes and the extract was separated. Finally, the supernatant was filtered from a membrane filter and was prepared for use. 75 mL rinse solution was freshly prepared to be used in patients in 15 mL cups for single use and prepared again when it finished.

Measurements

The measurement is planned through the following method. The subjects were selected using simple lottery method from patients who are aged 10-13 years (mean age: 11.33) and have a clinical picture of

simple gingivitis. The same procedures were followed for all patients. The patients who have unknown allergies or idiopathic allergies were excluded from the study.

Saliva samples were collected before gargling, at the end of 5 m (T1), 1 h (T2) and was transferred to laboratory as soon as possible. The differences were calculated within 5-60 m (T3) (Figure 1).

CHX group; Saliva samples were obtained from all patients (baseline) and then patients rinsed their mouth with CHX (0.2% of CHX solution, klorhex, drogsan, Ankara, Turkey). After 5 min, a new saliva sample was taken to count SM and the last saliva sample was taken at the end of 1h.

LICORICE group; Saliva samples were obtained from all patients (baseline) and then, the patients rinsed their mouth with freshly prepared licorice (in 15 mL cups for 1 min) and then two saliva samples were obtained at the end of 5 min and 1 h.

SALINE group; Saliva samples were obtained from all patients (baseline) and then, after rinsing their mouth with saline, the saliva samples were taken at the end of 5 min and 1 h to see any decrease in SM count.

After collecting saliva samples, the samples were sent to microbiology laboratory immediately.

Streptococcus Mutans Count

A saliva sample of 0.01 mL was obtained and added to a physiologic serum solution of 9.99 mL. A 0.01 mL of the obtained suspension was taken using a sterile plastic loop and was cultured in Difco™ Mitis Salivarius Agar (Becton, Dickinson and Company, Sparks, MD, USA). The agars were incubated for 24-48 h in an environment with 5% CO_2 at 36.5 ^{O}C. Plaques were evaluated following incubation and counts of the growing colonies were performed in colony forming ünits/mL^{-1} (CFU mL^{-1}). Elevated colonies that grew in the plaques that were faded blue in color and had a granular ground-glass appearance were accepted as SM. Colonies evaluated to be SM in the agars were confirmed using Microflex LT MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) and BD Phoenix 100 system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) and Streptococcus definition panels (BD Phoenix SMIC/ID-11 Becton Dickinson, Sparks, MD, USA).

Statistical Analysis

After counting the SM colonies, the data were enrolled and the percentages were calculated by the ratio of the decreases in SM count. The data was enrolled with SPSS 17. The compliance of normal distribution of data was performed by Shapiro Wilk test. Kruskal-Wallis Mann-Whitney U test was performed with Bonferroni correction because of non-compliance with a normal distribution. Variations by time were performed with Friedman Wilcoxon signed-rank test by Bonferroni correction. A p value of 0.05 was referred statistically different.

Results

Table 1 shows the minimum, maximum and median CFU of the groups. For the first 5 min (T1), CHX caused 100% decrease in some samples and CHX showed significantly different decreases in SM count when compared with the other groups. CHX and licorice showed 100% decrease in some samples in T2. CHX and Licorice showed significantly higher decreases in binary comparisons of the groups (Table 2). CHX showed significantly different decreases in T1 and T2 group but there were no significant differences in T3 between CHX and Licorice ($p>0.05$). Decreases were seen in all samples of CHX and Licorice groups (Figure 2). The rankings of reducing of the number of bacteria colonies were CHX>Licorice>Saline in T1 and T2 but there were no significant differences in T3 between CHX and Licorice ($p>0.05$). Licorice and CHX decreased SM count 100% in some samples (Figure 3).

Table 1. The minimum, maximum, mean and standard deviations of the groups

Times	T1			T2			T3		
Groups	min	max	Mean + SD	Min	max	Mean + SD	min	max	Mean + SD
SF	5.26	44.82	23.14+11.27	7.69	37.93	20.08+10.71	0	42.85	11.03+10.27
Licorice	7.31	67.30	39.70+16.18	37.50	100	69.18+14.88	5.08	60	29.47+17.01
CHX	18.75	100	69.26+20.86	53.84	100	89.33+12.88	0	57.81	20.87+12.92

SD: Standard deviation, CHX: chlorhexidine, SF: Substandard and falsified, max: Maximum, min: Minimum

Table 2. Binary comparisons of the groups									
	Saline			Licorice			CHX		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
Saline	-	-	-	0.001	0.000	0.000	0.000	0.000	0.003
Licorice	0.001	0.000	0.000	-	-	-	0.000	0.000	0.167*
CHX	0.000	0.000	0.003	0.000	0.000	0.167*	-	-	-
CHX: Chlorhexidine, *: there were no significant differences in T3 between CHX and licorice									

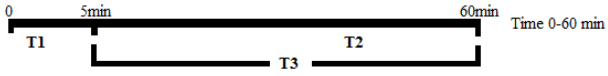

Figure 1. Timing of the groups, T1: 0-5 min, T2: 0-60 min, T3: 5-60 min

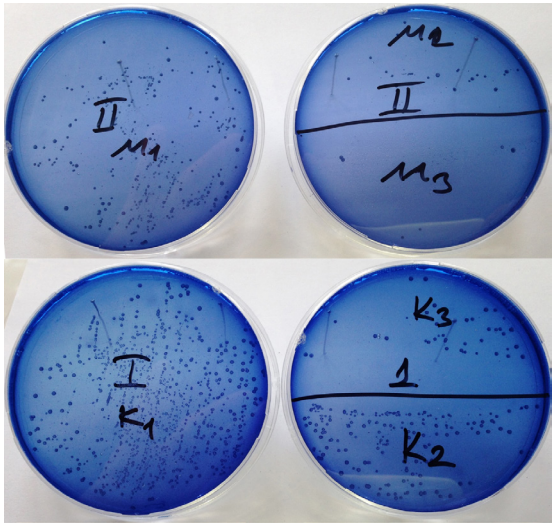

Figure 2. Chlorhexidine (CHX) and licorice showed decreases in all samples (M_1: Licrorice T1, M_2: Licorice T2, M_3: Licorice T3, K_1: CHX T1, K_2: CHX T2, K_3: CHX T3)

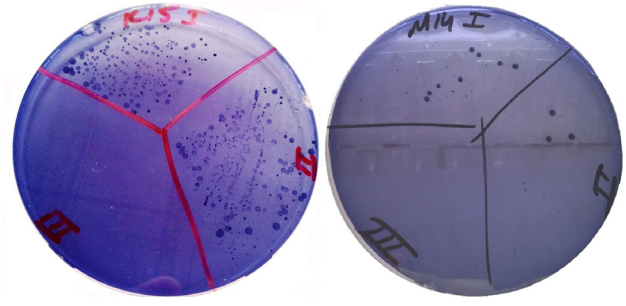

Figure 3. Shows 100% decreased amount of streptokok mutans [M_1: Licorice T1, M_2: Licorice T2, M_3: Licorice T3, K_1: Chlorhexidine (CHX) T1, K_2: CHX T2, K_3: CHX T3]

Discussion

The main purpose of dentistry is to help humans to maintain oral health throughout their life (2). The most common dental problems were caused by microorganisms and these microorganisms are responsible in pulpitis, infection mediated necrosis and their extension to the periapical tissue. Removing dental plaque or killing oral bacteria with antibacterials are common anti-microbial strategies to treat dental caries (21,22).

CHX is used for chemical plaque control and inhibition of bacterial colonization to tooth surfaces. In the oral cavity, CHX is an effective antibacterial agent and has effect on a wide range of microorganisms. Being effective on some SM species, CHX is used to prevent and reduce carious lesions. CHX reacts directly with the surface of microbial cell, destroys the cell membrane integrity, penetrates the cell, and precipitates the cytoplasm leading to cell death (15,23). CHX or CHX containing oral health products has the strongest antimicrobial action against SM.

As it is shown in several clinical studies that CHX gluconate is a cationic bisguanide which has a broad-spectrum antimicrobial action and has effectiveness in decreasing the formation of dental biofilm (plaque) and gingivitis (24,25). However, CHX has some side effects likemain bitter taste and the formation of extrinsic stains on the teeth and tongue, increased risk of caries due to fermentation and alcohol content, discoloration, altered taste perception, metallic taste, staining of teeth and cytotoxic effects on cells (15,23). All these disadvantages have led current research to more natural and biocompatible agents like herbal medicines (26).

History of herbal medicines usage be rooted from ancient civilization and have been used for many years where their role as a primary source of medicine has been evident. In developing countries herbal

medicines are still the mainstay of about 75-80% of the population for primary health care because of better cultural acceptability, better compatibility with human body, and fewer side effects. Hence, studies are being carried out to discover new alternate plant-based bioactive compounds which will be safer, easily available, and substitute standard pharmaceutical remedies (21-23,27).

Antimicrobial activity of licorice was shown in many studies (28,29). It is used for many purposes like antibacterial agent, for ulcerous lesions, mouth wash, endodontic infections, and periodontitis. It demonstrates anti-inflammatory, antimicrobial, anticarcinogenic and hepatoprotective effects (23,27,28,30-32). One of the aims of using licorice is to reduce the bacteria colonies that lead dental caries and, for this purpose, licorice was added into lollipop, gargling solutions and gels.

In this study, licorice was used as gargling solution. There are two forms of licorice gargling solution. One is aqueous licorice form and the other is alcoholic licorice form. Ajagannanavar et al. (21) declared that alcoholic root extract of licorice was superior to aqueous form and CHX. Sedighinia et al. (27) declared that the ethanolic extract of Glycyrrhiza glabra had promising macrophage inhibitory cytokine value against all oral bacteria, especially *S. mutans*, *A. viscosus*, and *E. faecalis*. Ahn et al. (23) found that three purified compounds that were isolated from ethanol-extracted licorice root, were less cytotoxic to normal human gingival fibroblast cells than CHX. Jain et al. (15) concluded that alcohol was a better solvent than water and that the reduction in colony counts of ethanolic licorice group was more significant than the control groups. In line with the results of these studies, alcoholic form of licorice was preferred in this study.

CHX, has been considered to be the gold standard of oral therapies due to its prolonged broad spectrum antimicrobial property, but is accompanied by altered taste perception, metallic taste, and staining of teeth. CHX also possesses the unique property of substantivity, pertaining to which it has slow, sustained release in the oral cavity and hence, prolonged action (15,24,33). CHX was one of the mouthwashes used in this study. CHX showed more decrease in SM count than the other mouthwashes in T1 and T2 and the decreases were statistically different. However in T3, licorice showed 30% and CHX showed 19.37% decrease, though there were no significant differences between both groups. This has led to a conclusion that licorice showed its effect in a long-time period. The authors declared that one of the limitations of this study was that the study was completed in one hour and long-term follow up studies are needed to support this conclusion.

In some samples, both licorice and CHX decreased SM count 100% and this result indicated that the licorice mouthwash is a dose dependent material which shows its effectiveness by containing glycyrrhizin. Glycyrrhizin is the most important ingredient of licorice which might be in a high concentration and provide the antimicrobial effect of licorice (15,28). The high concentration of glycyrrhizin (5%, 10%) slightly inhibited bacterial growth, but completely abolished plaque formation (34). Soderling et al. (28) declared that the liquorice extract inhibited acid production effectively *in vivo* with concentrations ranging from 2.5 to 10%. Glycyrrhiza glabra extract containing 7-7.5% glycyrrhizin was found advantageous in terms of cytotoxicity because 87% of periodontal ligament fibroblasts were alive after 48 h (30). Another limitation of this study is that the ratio of glycyrrhizin could have been calculated initially, but being an *in vivo* study, could give the authors more opinions for further studies.

Study Limitation

There are some disadvantages of CHX and this study shows herbal products can be alternatives to this kind of products.

The importance of herbal products are increasing and this study shows licorice can be an alternative to CHX.

If effective dose of active substance of licorice is detected and prepared as a gargling solution, the patients will survive from side effects of CHX.

Conclusion

The results of this study indicated that licorice might be a useful tool for dental procedures and further studies are needed to learn more about the dose of licorice, the ratio of glycyrrhizin and the duration of dental therapy.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Cumhuriyet University Clinical Research Ethic Committee (2014-02/15).

Informed Consent: Informed consent forms were taken both from patients and parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Original Article / Özgün Araştırma

Evaluation of the Relationship Between Malocclusion and the Periodontal Health, Caries, Socio-economic Status of Children

Çocuklarda Görülen Malokluzyonlar ile Periodontal Sağlık, Diş Çürükleri ve Sosyo-ekonomik Durum Arasındaki İlişkinin Değerlendirilmesi

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Keywords
CPITN, DMFT, malocclusion, orthodontic treatment need

Anahtar Kelimeler
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Abstract

Objective: In this study, it was aimed to evaluate the relationship between malocclusions and various factors such as periodontal treatment needs, dental caries, anterior segment crowding and parental socio-economic status of 12–14 year-old children.

Materials and Methods: Classification of malocclusions of 534 patients aged 12-14 years who applied to our clinic in our study was done according to Angle malocclusion classification. Periodontal treatment requirements were assessed using community periodontal index of treatment needs (CPITN); dental caries were evaluated by decay, missing, filled teeth (DMFT). Statistical analysis was performed in SPSS Statistics Version 12.0 software package. $P<0.05$ was considered statistically significant.

Results: The mean DMFT score of the children in the study group was 4.318 ± 3.14. The most common malocclusion was class 1 malocclusion (55.1%). The differences between mean DMFT scores and malocclusion classifications were not statistically significant ($p>0.05$). According to the CPITN, individuals with healthy periodontal disease (CPITN 0) accounted for 24.9% of patients. It was seen that only 6.4% of the patients without anterior segment crowding had CPITN 2 score. It was observed that the CPITN 0 score decreased as the anterior segment crowding increased. It was found that the correlation between CPITN scores and anterior segment crowding was statistically significant ($p<0.05$). However, the relationship between malocclusion classifications was not statistically significant ($p>0.05$). There was no statistically significant relationship between parental socio-economic status and malocclusion classifications of children ($p>0.05$).

Conclusion: In our study, there is no correlation between malocclusions and dental caries. However, it has been observed that the lower anterior segment crowding are detrimental to periodontal health, laying the groundwork for the development of periodontal diseases. Oral health care and early interventions (preventive and preventive programs) are thought to help prevent orthodontic problems that can occur.

Öz

Amaç: Bu çalışmada, 12-14 yaşları arasındaki çocuklarda maloklüzyonların periodontal tedavi gereksinimleri, diş çürükleri, ön segmentte yer darlığı ve ebeveynlerin sosyoekonomik durumları gibi birçok faktörle olan ilişkilerinin değerlendirilmesi amaçlanmıştır.
Gereç ve Yöntemler: Çalışmamızda, kliniğimize başvuran 12-14 yaşları arasındaki 534 sağlıklı hastanın malokluzyonlarının sınıflandırılması Angle malokluzyon sınıflamasına göre yapılmıştır. Periodontal tedavi gereksinimleri toplumda periodontal tedavi gereksinimi indeksi (CPITN), diş çürükleri çürük, kayıp, dolgulu dişler (DMFT) indeks değerleri kullanarak değerlendirilmiştir. İstatistiksel analizler SPSS Statistics Version 12 paket programında yapılmıştır. P<0,05 istatistiksel olarak anlamlı kabul edilmiştir.
Bulgular: Çalışma grubundaki çocukların ortalama DMFT değeri 4,318±3,14 olarak saptanmıştır. En yaygın maloklüzyonun, sınıf 1 malokluzyon (%55,1) olduğu görülmüştür. Ortalama DMFT değeri ile maloklüzyon sınıflamalarının arasındaki farklılıklar istatistiksel olarak anlamlı bulunmamıştır (p>0,05). CPITN'e göre, sağlıklı periodonsiyuma (CPITN 0) sahip olan bireyler hastaların %24,9'unu oluşturmuştur. Ön segmentte yer darlığı olmayan hastaların sadece %6,4'ünün CPITN 2 değerine sahip oldukları görülmüştür. Ön segmentte yer darlığı artıkça CPITN 0 değerinin azaldığı gözlenmiştir. Ön segmentte yer darlığı ile CPITN değerleri arasındaki ilişkinin istatistiksel olarak anlamlı olduğu görülmüştür (p<0,05). Ancak maloklüzyon sınıflamaları arasındaki ilişki istatistiksel olarak anlamlı bulunmamıştır (p>0,05). Ailelerin sosyo-ekonomik seviyeleri ve çocukların maloklüzyon sınıflamaları arasında da istatistiksel olarak anlamlı ilişki bulunmamıştır (p>0,05).
Sonuç: Çalışmamızda, malokluzyon ile diş çürükleri arasında ilişki görülmemiştir. Ancak, alt ön dişlerdeki çapraşıklıkların, periodontal sağlık üzerinde zararlı etkileri olduğu, periodontal hastalıkların oluşmasına zemin hazırladığı gözlenmiştir. Ağız sağlığı bakımları ve erken yaşlardaki müdahalelerin (koruyucu ve önleyici programlar) oluşabilecek ortodontik problemlerin önlenmesine yardımcı olabileceği düşünülmektedir.

Introduction

Malocclusion is defined as the absence of an association between the upper and lower arches and abnormal alignment of the teeth. It has led to an increased interest in orthodontic treatment in many countries. Malocclusion can increase the risk of dental trauma, caries, periodontal problems, and oral dysfunctions such as chewing, swallowing, and talking difficulties (1).

Many factors can affect the severity of malocclusion and the desire to receive orthodontic treatment in individuals. One of these factors is the socio-economic status of the patients/parents (2). Studies have shown that the incidence of malocclusion severity and orthodontic treatment need is high among individuals with low socio-economic status (3-5). The lack of social protection programs in the low socio-economic classes has been reported to be one of the main causes. In addition, high caries rates and the early loss of primary teeth, which may result from irregular dental visits, can cause the displacement of teeth and crowding (5,6).

One of the most common types of malocclusions that affect the aesthetic appearance, function, and quality of life of the patients is dental crowding (1). Irregularities are generally observed 40-58% in the lower incisors in retention areas, especially in individuals with poor oral hygiene habits. In these areas, plaque accumulation can increase and caries occur, this affects periodontal health negatively (7-12). When malpositions with adverse effects are observed, orthodontic treatment should be provided to redirect occlusal forces. Consequently, occlusal trauma, which may also affect periodontal health, can be prevented.

Several epidemiological studies have been conducted in communities with different ethnic origins to evaluate the effects of malocclusion on periodontal health (1,13,14). However, there are limited studies evaluating the relationship between malocclusion and the socio-demographic factors, caries, and periodontal status of children/adolescents in Turkey (10). These studies are important for evaluating the risk of caries in patients, identifying malocclusion and patients who require early preventive orthodontic treatment, and initiating treatments. Furthermore, the findings can be applied to improve oral hygiene in communities and reduce the costs of orthodontic treatment.

With more detailed information from this study results, we expect to identify malocclusion prevalence and associated conditions of malocclusion in 12-14-years-old children. This might help in understanding maloclussion occurrence and also assist public health interventions.

This study was designed to determine the relationship between malocclusion and the periodontal treatment requirements, dental caries,

anterior segment crowding, and parental socio-economic status of 12-14 year-old children. Our hypothesis was that malocclusion was associated with these parameters.

Materials and Methods

Required approvals from the Süleyman Demirel University Faculty of Medicine Clinical Studies Ethics Council were obtained for this study (approval number: 2014/93). The patients signed an Informed Consent Form, as established by the ethical guidelines. The study population consisted of 534 healthy children (233 males, 301 females) between 12 and 14 years of age who applied to our clinic in the period of June to December, 2014. It has been noted that individuals participating in the study were selected to have no orthodontic treatment history in the past, to be individuals with no syndromes that would affect the development of craniofacial structures, to have no orthognathic surgery, and not to be disabled individuals.

To evaluate the incidence of dental caries among the children, the number of decayed, missing, and filled teeth were recorded according to the decay, missing, filled teeth (DMFT) system (15). Angle's malocclusion classification was used to assess molar relationship (16). In order to determine the relationship between socio-economic status and malocclusion classification, the self-reported monthly income levels of the families were divided into three groups: <1000₺, 1000-3000₺, and >5000₺. The lower and upper anterior segment crowding was assessed as follows: 0 - if there is no space; 1 - if only one segment is scored; 2 - if both segments are scored (17). To determine periodontal status and treatment needs, community periodontal index of treatment need (CPITN), which is recommended by the World Health Organization (WHO), was used. The highest score was recorded for each tooth according to the CPITN criteria. The highest score was selected as the CPITN score of each individual, and periodontal treatment needs were determined. The CPITN scores were set so that 0=healthy, 1=bleeding on gentle probing, 2=calculus or other plaque-retentive factors, 3=shallow pocketing of 4-5 mm, and 4=deep pockets of 6mm or more (18).

Statistical Analysis

The data were analyzed using SPSS for Windows (SPSS-Statistical Package for Social Science, Software Version 12, SPSS Inc., Chicago, IL, USA). The effects of CPITN score on crowding in the anterior segment and malocclusion classification were examined using the chi-square test. In addition, the chi-square test was used to evaluate malocclusion classification according to age, gender, socio-economic status, and DMFT scores. The Kruskal-Wallis test was used to evaluate the data obtained from the DMFT in terms of age. Student's t-test was used to analyze data on DMFT characteristics according to gender. Levels of statistical significance were set at $p<0.05$.

Results

In the study, 534 children between 12 and 14 years of age were evaluated. The mean age of the children was 13.01±0.04. The distribution of patients according to age was as follows: 12 years, 170 (31.8%); 13 years, 189 (35.4%); 14 years, 175 (32.8%). There was no difference in the sex distribution of all age groups.

The mean DMFT score was 4.32±3.14. In addition, 12.2% of the study group consisted of children with a DMFT score of 0. The mean DMFT scores were 3.61±2.66 for 12-year-old children, 4.46±3.06 for 13-years-old children, and 4.86±3.52 for 14-year-old children; the scores were increased with age. Although the mean DMFT score of females (4.39±3.16) was higher than that of males (4.23±3.11), the differences between gender and the mean DMFT scores were not statistically significant ($p>0.05$).

In the study, class 1 malocclusion (55.1%) was the most common malocclusion. Class 2 (23% class 2 div 1, 13.7% class 2 div 2) was observed in 36.7% of the children, and class 3 malocclusion was observed in 8.2% of the children. The lowest mean DMFT scores were found among children with class 2 div 2 malocclusion, whereas the highest scores were found among children with class 1 and class 3 malocclusions. Class 1, class 2 div 1, and class 2 div 2 malocclusions were more common among females than males, whereas class 3 malocclusion was more common among males. There was no statistically significant relationship between gender and malocclusion ($p>0.05$) (Table 1). Moreover, the relationship between age and malocclusion classification was not statistically significant ($p>0.05$). The differences between mean DMFT scores and malocclusion classification were not statistically significant ($p>0.05$) (Table 2).

The majority of children (83.14%) had low-income families (<1000₺, 1000–3000₺). In the study, 62.2% of the children with a monthly family income level of 3000" or more had class 1 malocclusion, and 2.2% had class 3 malocclusion. There was no statistically significant relationship between the socio-economic levels and malocclusion classification of children (p>0.05)

According to the CPITN, children with healthy periodontal status (CPITN 0) accounted for 24.9% of the study group. Despite the absence of calculus and iatrogenic irritation, there was bleeding (CPITN 1) in 67% of the patients during scaling, and both iatrogenic irritation and supragingival/subgingival dental plaque (CPITN 2) were observed in 8.1% of the patients. Patients with CPITN 3 and CPITN 4 were not evaluated.

Only 6.4% of the patients without anterior segment crowding had CPITN 2 score. CPITN 0 score were decreased with increasing crowding in the anterior segment. The relationship between CPITN scores and crowding was statistically significant in the anterior segment (p<0.05) (Table 3). In the study, 55.8% of children with CPITN 2 and 54.8% of those with CPITN 0 had class 1 malocclusion. It was found that only 8.67% of children with class 2 malocclusion required oral and dental care education as well as scaling. The relationship between CPITN scores and malocclusion classification was not statistically significant (p>0.05) (Table 4).

Table 1. The distrubition of malocclusion classification according to gender

Gender	Angle malocclusion classification									
	Class 1		Class 2 div 1		Class 2 div 2		Class 3		Total	
	n	%	n	%	n	%	n	%	n	%
Female	168	55.8	72	23.9	41	13.6	20	25.8	301	56.4
Male	126	54.1	51	21.9	32	13.7	24	13.5	233	43.6
Total	294	55.1	123	23	73	13.7	44	8.2	534	100

x^2: chi-square, p=0.486, div: Division

Table 2. The relationship between malocclusion classification and mean decay, missing, filled teeth scores

Malocclusion classification	n	Mean DMFT	Standard deviation	Standard error
Class 1	294	4.510[a]	3.0999	0.1808
Class 2 div 1	123	4.407[ab]	3.2538	0.2934
Class 2 div 2	73	3.274[b]	2.6628	0.3117
Class 3	44	4.523[a]	3.5666	0.5377
Total	534	4.318	3.1408	0.1359

DMFT: Decay, missing, filled teeth, div: Division

Table 3. The relationship between anterior segment crowding and community periodontal index of treatment needs scores

Anterior segment crowding	The community periodontal index of treatment needs (CPITN)								x^2
	CPITN 0		CPITN 1		CPITN 2		Total		
	n	%	n	%	n	%	n	%	
0	79	59.4	140	39.1	15	34.9	234	43.8	22.114
1	28	21.1	100	27.9	8	18.6	136	25.5	
2	26	19.5	118	33	20	46.5	164	30.7	
Total	133	24.9	358	67	43	8.1	534	100	

x^2: chi-square, p=0.000, CPITN: Community periodontal index of treatment needs

Table 4. The relationship between malocclusion classification and CPITN scores

CPITN	Angle malocclusion classification										
	Class 1		Class 2 div 1		Class 2 div 2		Class 3		Total		x^2
	n	%	n	%	n	%	n	%	n	%	
CPITN 0	73	54.9	20	15	24	18	16	12	133	24.9	1.631
CPITN 1	197	55	92	25.7	43	12	26	7.3	358	67	
CPITN 2	24	55.8	11	25.6	6	14	2	4.7	43	8.1	
Total	294	55.1	123	23	73	13.7	44	8.2	534	100	

x^2: chi-square, p=0.091, div: Division, CPITN: Community periodontal index of treatment needs

Discussion

This cross-sectional study was conducted in 12–14-year-old children. Because, the eruption of permanent teeth completes nearly at the age of 13 and the clinical diagnosis of the type and extent of malocclusion is best made at this age group (17). Also, ın a study, when the patients who applied to the clinic for orthodontic treatment were compared according to their dentition periods (6-9, 10-12 and ≥13 years), it was observed that the most frequent patients were 13 years (19). Because of these reasons, we decided to evaluate the relationship between malocclusion and related various factors in children aged 12-14 years.

One of the methods widely used in epidemiological studies of malocclusions is Angle's malocclusion classification (20). In our study, according to Angle's classification, 55.1% of children had class 1 malocclusion; this result was similar to that of a study performed with 100 children (10-12 years of age) in Turkey (21). However, recent studies have shown that the most common malocclusion in adolescents is class 2 malocclusion in Turkey (22-25). Nevertheless, when the literature review was done, data on the prevalence of malocclusion are limited (26-28).

Since socio-economic differences are an important factor in Turkey, families were separated into groups according to monthly income levels, and their effects on malocclusion were examined in our study. Some studies have reported that children at low socio-economic levels have more severe malocclusions and poor oral/dental health (20,29,30). However, there are also studies that have reported that the severity and classification of malocclusion are not different based on socio-economic status (31-33). In our study, there was no statistically significant relationship between the socio-economic levels and malocclusion classification of children reform of the health care systems to provide government-subsidized treatment according to the past years has made it easier for the low-income families to benefit protective and preventive dental programs in early dentition period of their children from the public hospitals. Thus, this could contribute the prevention of malocclusion in children. If an identical study is repeated in a few years after changes to the socio-economic environment in the overall population, different results might be observed. One of the etiologic factors that can cause the space loss in the dental arch and malocclusions, both in the mixed and permanent dentition, is dental caries (31-33). Children with dental caries (DMFT>0) were almost twice as likely to have class 2-3 malocclusion compared with children without dental caries (DMFT=0) (8). On the other hand, in a study of 12-year-old children in India in 2015, no association was found between malocclusion and caries (9). In our study, the differences between mean DMFT scores and malocclusion classification were not statistically significant (p>0.05). Because, the DMFT index is inadequate when compares dental caries and malocclusion. It does not distinguish between a small, non-cavitated lesion and a large cavitated lesion with loss of tooth structure. It includes many lesions that are non-cavited and therefore can have no more effect on malocclusion. Individuals with a moderate and high risk for caries have increased the orthodontic treatment needs (34). Indeed, according to Dental Health Component, children with high DMFT scores

have increased orthodontic treatment needs (35,36). According to Dental Aesthetic Index (DAI), children between the ages of 11 and 15 with a DAI score of >35 were reported to have more dental caries than other children (37). The prevalence of severe caries (DMFT>8) was observed to increase from 10.8% to 50% when DAI scores were increased (38). The early prevention and treatment of caries will help to reduce orthodontic treatment needs.

Malocclusion is also an important factor in the etiology of periodontal disease. Irregularities in the lower anterior teeth can have adverse effects on the periodontal health of the teeth, increase plaque accumulation, and lead to periodontal diseases (39). Gingivitis was observed to be at a high level in patients with malocclusion compared with those without malocclusion (40). Conversely, in a study of children with a mean age of 12.38±0.75, there was no correlation between periodontal disease and irregularities of the teeth when oral hygiene was good (41). In another study of children aged 10-18 years, malocclusion severity was not associated with periodontal status between groups with an overjet of more than 6 mm, a deep bite of more than 6 mm, and posterior unilateral or bilateral crossbite (42). Similar to the results of these studies, there was no statistically significant relationship between CPITN scores and malocclusion classification in our study ($p>0.05$). Due to differences between the sample groups and the methods used, different results could be obtained when evaluating the relationship between periodontal status and malocclusion. In addition, it is possible that the CPITN measures the periodontal treatment needs of the entire jaw and masks local periodontal problems with healthy areas (10).

When the relationship between treatment needs and oral hygiene conditions (plaque, amount of calculus, gingivitis, and pocket depth) was assessed, no relationship was found (43,44). In a study in Nigeria, the association between the DAI and CPITN scores of patients with a mean age of 15.8±7.5 was not statistically significant (45). In contrast, a study in Turkey involving 836 patients between 11 and 14 years of age has reported a close relationship between treatment priority index TPI and CPITN scores (10).

Occlusal irregularities and crowding may be responsible for periodontal diseases (46). Although there was a correlation between irregularity and gingivitis scores, the amount of plaque accumulation and the degree of irregularity were not clinically significant (43). Studies have reported a correlation of malpositions in the lower arch, irregularities in the upper arch, and deep bite with CPITN scores (14,47). For teeth with occlusal irregularities, there was a significant increase in the depth of scaling every year; however, there was no significant increase in scaling depth for teeth without occlusal irregularities (48).

In this study, only 6.4% of the patients without anterior segment crowding had a CPITN score of 2. CPITN 0 scores were decreased with increasing crowding in the anterior segment. The positive relationship between the degree of irregularity and the severity of gingival inflammation may be attributed to the bad oral hygiene of the patients, which can lead to dental plaque formation and cause the onset of periodontal inflammation. Nevertheless, crowding would not contribute to gingivitis if the individual has good oral hygiene (46).

Conclusion

In the study, periodontal status was associated with anterior segment crowding but not malocclusion classification. However, malocclusion could cause an increase in plaque retention. In addition, ıt was concluded from the present study that malocclusion had no significant effect on dental caries and parental socio-economic status. Thus, the hypothesis of the present study was rejected.

Patients with malocclusion should be evaluated so as to facilitate oral health by minimizing inaccessible areas in the oral cavity. Assessment of the orthodontic treatment needs of children should be based not only on the severity of malocclusion features but also on the dentition period, and the age group of the children. Further studies involving large populations are necessary in different age groups, which requires increased attention regarding to prevent maloclussion.

Ethics

Ethics Committee Approval: Süleyman Demirel University Faculty of Medicine Clinical Studies Ethics Council (approval number: 2014/93).

Informed Consent: All patients included were informed about the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Original Article / Özgün Araştırma

Evaluation of Water Sorption-solubility and Surface Roughness of Different Bulk Fill Composite Resins

Farklı Bulk Fill Kompozitlerin Su Emilimi, Çözünürlük ve Yüzey Pürüzlülüklerinin Değerlendirilmesi

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Abstract

Objective: This study aimed to investigate and compare the water sorption (WS), solubility (SO) and surface roughness (SR) of four bulk fill resin-based composites (RBCs), a conventional flowable RBC and a conventional hybrid RBC.

Materials and Methods: Disc-shaped specimens of 3 low-viscosity bulk fill RBCs (SureFil SDR flow, X-tra base, Filtek Bulk Fill flow), 1 high-viscosity bulk fill RBC (Tetric EvoCream Bulk Fill), 1 conventional low-viscosity flowable RBC (Filtek Ultimate flow) and 1 conventional hybrid RBC (Filtek Z250) (n=10) were prepared and immersed in distilled water for 28 days. Upon removal, specimens were weighed using an electronic scale to determine WS and SO based on weight gain/loss, and surface profilometry was performed to determine SR. Data were analyzed using one-way ANOVA and Tukey's post-hoc tests (p=0.05).

Results: WS and SO showed significant, positive correlations (r=0.612; p<0.001), and both varied significantly among the materials, with WS and SO values of both high-filled and low-filled bulk fill RBCs lower than their conventional counterparts. Moreover, SR values of both bulk and conventional flowable low-fill RBCs were significantly lower in comparison to the high-fill RBCs (p<0.05).

Conclusion: WS, SO and SR of RBCs are material-dependent and highly affected by filler loading and resin matrix composition. Bulk fill RBCs can be used in a large variety of clinical situations in line with the manufacturers' recommendations.

Öz

Amaç: Bu çalışmanın amacı dört farklı bulk fill kompozit rezin ile bir adet geleneksel akışkan kompozit ve bir adet geleneksel hibrit kompozitin su emilimi, çözünürlük ve yüzey pürüzlülüğü değerlerini karşılaştırmalı olarak incelemektir.

Gereç ve Yöntemler: Üç adet düşük viskoziteli bulk fill kompozit (SureFil SDR flow, X-tra base, Filtek Bulk Fill flow), bir adet yüksek viskoziteli bulk fill kompozit (Tetric EvoCream Bulk Fill), bir adet geleneksel düşük viskoziteli akışkan kompozit (Filtek Ultimate flow) ve bir adet geleneksel hibrit kompozit (Filtek Z250) kullanılarak disk şeklinde örnekler hazırlanıp distile suda 28 gün bekletilmiştir (n=10). Örnekler elektronik bir terazide tartılarak kütle kazanım ve kayıp değerlerine göre su emilimi ve çözünürlük değerleri hesaplanmıştır. Daha sonra yüzey pürüzlülüğü ölçümü için profilometre cihazı kullanılmıştır. Elde edilen veriler tek yönlü ANOVA ve Tukey post-hoc testleri ile analiz edilmiştir (p=0,05).

Bulgular: Su emilimi ve çözünürlük değerleri arasında pozitif korelasyon tespit edilmiştir (r=0,612; p<0,001), her iki parametre de materyaller arasında belirgin farklılık göstermiştir. Hem düşük hem de yüksek viskoziteli bulk fill kompozitler geleneksellerine kıyasla daha düşük su emilimi ve çözünürlük değerleri göstermiştir. Yüzey pürüzlülüğü açısından ise hem geleneksel hem de bulk fil akışkan kompozler, yüksek dolduruculara göre belirgin şeklide daha düşük pürüzlülük göstermiştir (p<0,05).
Sonuç: Su emilimi, çözünürlük ve yüzey pürüzlülüğü değerleri materyale bağlı özelliklerdir ve rezin matriksin yapısından ve doldurucu oranından önemli derecede etkilenirler. Üretici önerileri doğrultusunda bulk fill kompozitler klinikte geniş bir kullanım alanına sahiptirler.

Introduction

As a result of constant efforts by the industry to improve the properties of dental materials, several innovative restorative materials have been introduced for use in posterior dental restorations, including a new class of resin-based composite (RBC) materials known as "bulk fill RBCs"(1). Manufacturers of bulk fill composites claim that polymerization shrinkage stress has been reduced and depth of cure improved sufficiently to allow for placement of these materials in layers of up to 4 mm. The improvements in material characteristics have been achieved through various strategies - e.g. using macrofillers to increase material translucency, incorporating particles with a low elastic modulus and otherwise modifying resin composition, as well as using alternative photoinitiator systems (2,3). In contrast to the first versions of bulk fill materials, which had low viscosity and required an additional, final layer of conventional RBC, the recently introduced bulk fill RBCs have a higher viscosity and don't require capping with conventional RBCs (4). Most low-viscosity, flowable bulk fill RBCs are indicated by their manufacturers for use as either a liner or base in class 1 and 2 cavities (1). In addition, some flowable bulk fill RBCs are indicated for use in class 3 and 5 cavities as well as in the restoration of minimally invasive cavity preparations and as pit-and-fissure sealants (5,6). High-viscosity bulk fill RBCs are indicated for restorations in the posterior region (classes 1 and 2, including the replacement of individual cusps), class 5 restorations and reconstructive build-up (3). Regardless of their properties, all restorative materials are subjected directly to saliva and other altering conditions in the oral environment, making water sorption (WS), water solubility (SO) and surface roughness (SR) important parameters in determining their clinical longevity (7-9). This study measured the WS, SO and SR of 4 bulk fill RBCs and compared them to those of a conventional flowable RBC and a conventional hybrid RBC. The null hypotheses were that:

1. WS, SO and SR of the tested bulk fill RBCs would not differ from those of their conventional counterparts; and

2. WS, SO and SR properties of low-fill RBCs would not differ from those of high-fill RBCs.

Materials and Methods

Test Materials

The study was conducted with 6 commercially available RBCs, including 3 low-viscosity flowable bulk fill RBCs, 1 high-viscosity bulk fill RBC, 1 conventional low-viscosity flowable RBC and 1 conventional high-viscosity hybrid RBC. Material formulations and manufacturers are listed in Table 1.

Water Sorption and Solubility

Specimens (n=10 per group) were prepared using 2 mm depth x 10 mm diameter teflon molds. Molds were filled with composite, placed between two glass microscope slides, each about 1 mm thick, and pressed by hand to extrude excess material. A light emitting diode light-curing unit, (Elipar Free Light II, 3M/ESPE, St. Paul, MN, USA) was used to deliver 1.200 mW/cm^2 irradiation to each specimen. Light intensity was checked between each application using a calibrated radiometer. Specimens were irradiated from both the top and bottom surfaces for 20 s each, with the light tip -9.5 mm diameter - in direct contact with the microscope slides. After curing, the specimens were released from the molds, extruded material was removed using abrasive paper (Phoenix Beta, Buehler, Germany), and debris was cleared away using a dust blower. Specimens were placed in a vacuum desiccator and dried at 37±1 °C for 22 hours, transferred to a second desiccator and further dried at 23±1 °C for 2 hours, and then weighed to an accuracy of 0.0001 g, using a digital scale (Precisa XB 220 A, Zurich, Switzerland). The process was repeated

until a constant mass value was obtained (i.e. mass change of ≤0.1) on the display of the scale and recorded as "m_1". Specimens were then immersed in 10 mL distilled water in individual containers at 37±1 °C for 28 days, removed, gently dried with absorbent paper and weighed again to obtain to evaluate the weight after immersion and recorded as "m_2". Using the same protocol described above, specimens were reconditioned in desiccators until a constant mass was obtained again to evaluate the mass loss after immersion and recorded as "m_3". Percentages of WS and SO were calculated for each specimen according to the following equations: $WS=100x(m_2-m_1)/m_1$), $SO=100x(m_1-m_3)/m_1$).

An additional 10 specimens per group were prepared and polymerized as described above. Following polymerization, specimens were stored in distilled water at 37 °C for 24 h, removed and finished/polished using a series of aluminum oxide discs (Sof-Lex, 3M ESPE, St. Paul, MN, USA) for 15 s per disc (coarse medium, fine, superfine) in the same direction without water cooling. All preparations were performed by a single investigator. Polished specimens were rinsed in distilled water and allowed to dry again for 24 h in the room temperature (23 °C) before the average SR measurement. Roughness measurements were taken at 3 different locations per specimen from the top surfaces using a surface profilometer

Table 1. Materials used in the present study

Product	Type	Resin system	Filler (wt%), (vol%)
Filtek-bulk fill flowable, 3M ESPE, Germany	Low viscosity bulk fill	Bis-GMA, UDMA, Bis-EMA, TEGDMA, procrylat resin	64.5%, 42.5%
SureFil SDR flow, Dentsply Caulk, Milford, DE, USA	Low viscosity bulk fill	Modified UDMA, Bis-EMA, TEGDMA	68%, 44%
X-tra base, VOCO, Germany	Low viscosity bulk fill	Bis-EMA, EBPADA	75%, NA
Tetric EvoCeram bulk fill, Ivoclar Vivadent, Schaan, Liechtenstein	High viscosity bulk fill	Bis-GMA, UDMA, Bis-EMA,	77%, 60-61%
Filtek™ Supreme XTE, 3 M ESPE, Germany	Conventional flowable RBC	Bis-GMA, TEGDMA, Bis-EMA, procrylat resin	65%, 55%
Filtek Z 250, 3 M ESPE GmbH, Germany	Conventional hybrid RBC	UDMA, Bis-GMA, Bis-EMA, TEGDMA	82%, NA

NA: Stands for not available, UDMA: Urethane dimethacrylate, Bis-EMA: Bisphenol A ethoxylate dimethacrylate, TEGDMA: Triethylene glycol dimethacrylate, Bis-GMA: Bisphenol A glycidyl dimethacrylate, EBPADA: Ethoxylated bisphenolAdiacrylate, RBC: Resin-based composites

Table 2. Mean WS, SO and SR values of tested materials

Material	WS (%)	SO (%)	SR (Ra, µm)
Filtek Bulk fill flowable	$1.32±0.21^{BC}$	$0.08±0.03^{c}$	$0.07±0.02^{x}$
SureFil SDR flow	$1.03±0.34^{AB}$	$0.03±0.01^{b}$	$0.08±0.03^{x}$
X-tra base	$0.81±0.28^{A}$	$-0.07±0.03^{a}$	$0.07±0.02^{x}$
Tetric EvoCeram bulk fill	$1.07±0.14^{AB}$	$-0.05±0.01^{a}$	$0.38±0.17^{y}$
Filtek™ supreme XTE	$1.41±0.17^{C}$	$0.12±0.04^{c}$	$0.05±0.02^{x}$
Filtek™ Z250	$1.24±0.23^{BC}$	$0.12±0.04^{c}$	$0.32±0.12^{y}$

WS: Water sorption, SO: Solubility, SR: Surface roughness, Differences in superscript letters in the same column represent significant differences between groups (α=0.05)

(Mitutoyo SJ-400, Mitutoyo, Tokyo, Japan) with a speed of 0.1 mm/s, a 0.25 mm cutoff value and a 2 mm tracing length. SR values were calculated as the average of the 3 readings and recorded as "Ra" (μm).

Statistical Analysis

All statistical analysis was performed using SPSS for Windows, Version 12.0.1 (SPSS Inc, Chicago, IL, USA). Shapiro-Wilk's tests were performed and showed normality of distribution for all groups. Thus, data were compared using 1-way ANOVA followed by Tukey honestly significant difference and Tamhane's T2 post-hoc tests. Pearson correlation coefficients were calculated to analyze the correlation between WS and SO for each test material during 28 d water immersion. The level of significance was set at at 0.05.

Results

Means and standard deviations for the groups are presented in Table 2. The Pearson correlation coefficient analysis showed a positive, significant, correlation between WS and SO ($r=0.612$; $p<0.001$). X-tra base had the lowest WS value (0.81±0.28), and Filtek™ Supreme XTE had the highest WS value (1.41±0.17). Differences in WS between X-tra base, SureFil SDR flow and Tetric EvoCeram Bulk Fill and between Filtek™ Supreme XTE, Filtek Bulk Fill Flowable and Filtek™ Z250 were not statistically significant ($p>0.05$).

SO values varied significantly among the groups ($p<0.05$). The lowest SO values were detected in the X-tra base (-0.07±0.03) and Tetric EvoCeram bulk fill (-0.05±0.01) groups ($p<0.05$). The highest SO values were observed in the Filtek™ Supreme XTE (0.12±0.04) and Filtek™ Z250 (0.12±0.04) groups, but the differences in values among Filtek™ Supreme XTE, Filtek™ Z250 and Filtek Bulk Fill flowable group were not statistically significant ($p>0.05$).

SR values also varied significantly among the groups ($p<0.05$), as follows: Filtek™ Supreme XTE<Filtek Bulk Fill flowable=X-tra base<SureFil SDR flow<Filtek™ Z250<Tetric EvoCeram bulk fill.

Discussion

According to the study findings, WS, SO and SR values for some of the tested bulk fill RBCs were similar to those of their conventional counterparts; therefore, the first null hypothesis was partially accepted. Furthermore, viscosity had an effect on the SR of the bulk fill RBCs, but had no effect on their WS or SO; therefore, the second null hypothesis was also partially accepted.

The clinical performance of RBCs is dependent upon material characteristics as well as clinician proficiency. Until the last few decades, incremental layering had long been accepted as the standard technique for resin-composite cavity preparations (10). However, this technique has several drawbacks, namely the possibility of voids, contamination, or bond-failure between composite layers as well as the relatively extensive time required to place and polymerize each layer. In light of several recent studies suggesting that fewer increments and even bulk filling could be just as successful as the traditional layered approach (11,12), several manufacturers have developed posterior "bulk fill composite resins" that claim to have enhanced curing, shrinkage and other physical properties (2,3,5,6). Although various studies have been conducted that examine bulk fill RBCs, particularly in terms of polymerization (1,13-15), there is little information available regarding the WS, SO and SR of bulk fill RBCs.

WS and SO are important properties in assessing the clinical durability of dental restorative materials. According to ISO 4049:2009, WS is assessed by immersing dried specimens in distilled water for a certain period of time and by determining the amount of absorbed water by weight and the SO should be determined by weighing these specimens after drying them once again to constant weight (16). WS is a diffusion-controlled process that may to a certain extent reduce the polymerization shrinkage stress of RBCs (17), but may also result in chemical degradation of the material, leading to drawbacks such as filler-polymer matrix debonding and residual monomer release, and to mechanical degradation, leading to reductions in RBC restoration longevity (7) and potential allergic reactions in some patients (18). WS of RBC is affected mainly by material hydrophilicity and cross-linking of the network structure. Filler material, grain size, volume fraction and dispersion within the matrix as well as properties of the filler-matrix interface also play a role in the amount of solvent uptake during exposure (19-21). This study found the low-viscosity bulk fill composites X-tra base and Surefil SDR flow had significantly lower WS values when compared to their conventional counterpart.

This could be attributed to the higher filler-loading content of the bulk fill composites, given that an increase in filler ratio (by weight) entails a smaller polymeric matrix and hence a decrease in WS (21,22). The similar WS values of Filtek Bulk Fill Flowable and Filtek™ Supreme XTE can be explained by the similar filler loading and resin contents of the two materials, as noted by Alshali et al (21). In contrast to the low-viscosity RBCs tested, no significant differences in WS values were found between the high-viscosity bulk fill RBC TetricEvoCeram bulk fill and the high-viscosity conventional RBC Filtek™ Z250 ($p>0.05$). Although Filtek™ Z250 has higher filler load than Tetric EvoCeram bulk fill; the fillers used in Filtek™ Z250 are unsilanated, this could be expected to weaken the filler-matrix interface (21).

SO and WS are expected to show a correlation, since a solvent needs to penetrate a material in order for unreacted components to leach out. At the same time, conversion and cross-linking density play a major role in the relationship between sorption and SO (23). In fact, this study found correlations between WS and SO values for all RBCs tested ($r=0.612$). Thus, the same factors described above with regard to WS are also able to explain the findings of the present study with regard to SO. This study found negative SO values for X-tra base and Tetric EvoCeram bulk fill, indicating a reduction in the final volume when compared to the initial volume-which does not mean that the materials exhibited no SO, but simply that the amount of SO was less than the amount of WS of the materials. The negative values may mask the actual properties of the materials tested with regard to SO (24). Previous studies have also reported negative SO values for Tetric EvoCeram bulk fill (21,25). It has been suggested that this finding is related to incomplete dehydration and the formation of metal hydroxides within the RBC (21). SR is an important property that affects the appearance of RBC restorations. Profilometry using a contact stylus and determination of the Ra parameter has been a common method of quantitatively evaluating the SR of dental materials. A rough surface leads to increases in the accumulation of dental biofilm, residues and dyes, causing gingival irritation and a risk of secondary caries, and also diminishing restoration gloss, resulting in discoloration (26). The SR of RBCs is influenced by several material factors, including the type, shape, size and distribution of inorganic fillers. This study found no difference in the SR values of bulk fill RBCs when compared to their conventional counterparts ($p>0.05$). However, the high fill RBCs (Tetric EvoCeram bulk fill and Filtek™ Z250) had significantly higher SR values than the low-fill RBCs. An earlier study also reported high-fill RBCs to have higher SR values than low-fill RBCs (27). Moreover, previous studies have suggested that SR decreases in line with decreases in filler size (28) and increases in filler content (29). The nano-fill RBC Filtek Supreme XTE is characterized by a low filler-particle size and a low filler load, which could explain why it yielded the lowest Ra values of all the RBCs tested in this study. Roughness values of >0.2 µm can increase plaque accumulation, secondary caries risk and periodontal inflammation. In the present study, SR values of the high-fill RBCs Tetric EvoCeram bulk fill and Filtek™ Z250 were 0.38 µm and 0.32 µm, respectively which are above clinically acceptable values. Previous studies have also reported high Ra values for Filtek™ Z250 (30,31).

Conclusion

Dental practitioners need to keep abreast of the rapid developments in dental materials in terms of technical properties and clinical performance. Within the limitations of this in vitro study, bulk fill materials had WS, SO and SR values that were better or equal to their conventional counterparts, suggesting that they can, in fact, be used in the large variety of clinical situations recommended by their manufacturers.

Ethics

Ethics Committee Approval: It was not taken.

Informed Consent: It was not taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: N.G., Data Collection or Processing: N.G., E.Ş.T., Analysis or Interpretation: S.Ö., Literature Search: S.Ö., K.Y., N.G., Writing: N.G., E.Ş.T.

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

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Original Article / Özgün Araştırma

A Comparison of Chewing Movements of Individuals with Normal Occlusion by the Patients with Orthodontic Abnormalities During Treatment Progress

Normal Oklüzyonlu Bireylerle Ortodontik Anomali Tedavisi Gören Hastaların Çiğneme Hareketlerinin Kıyaslanması

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Abstract

Objective: Comparison of chewing movements of individuals with normal occlusion and those with orthodontic anomalies under treatment.

Materials and Methods: This is a prospective clinical study carried out on a total of 63 individuals, including 43 patients with malocclusion and an average age of 16.79 years, whose growth and development were partially complete and 20 individuals with normal occlusion and an average age of 24.77 years. Subjects with normal occlusion have not any orthodontic treatment history.

Results: There were significant differences in chewing occlusion times ($p<0.05$) and opening and closing times ($p<0.01$). Furthermore, significant differences were also found in modification results of class 1 ($p<0.05$) and class 2 ($p<0.01$) malocclusions.

Conclusion: Repositioning of the teeth in chewing movements obtained at the onset of orthodontic treatments tends to change within the end of the 6-month period from the onset of the treatment in individuals with malocclusion.

Keywords
Masticatory movements, orthodontic treatment, dental occlusion

Öz

Amaç: Normal oklüzyonlu ve tedavi altındaki ortodontik anomalili bireylerin çiğneme hareketlerinin karşılaştırılması.

Gereç ve Yöntemler: Bu çalışma, maloklüzyonlu 43 hasta ve ortalama yaşları 16,79 yıl olmak üzere, büyüme ve gelişmesi kısmen tamamlanmış, 20'si normal oklüzyonlu ve yaş ortalaması 24,77 yıl olan toplam 63 birey üzerinde yapılan prospektif bir klinik çalışmadır.

Bulgular: Oklüzyon süresinde ($p<0,05$) ve açılma ve kapanma oranlarında anlamlı fark bulundu ($p<0,01$). Ayrıca, sınıf 1 ($p<0,05$) ve sınıf 2 ($p<0,01$) malokluzyonların modifikasyon sonuçlarında da anlamlı farklılıklar bulunmuştur.

Sonuç: Ortodontik tedavinin başlangıcında elde edilen çiğneme hareketlerinde dişlerin yeniden konumlandırılması, maloklüzyonlu bireylerde tedavinin başlangıcından itibaren altı aylık sürenin sonunda değişme eğilimindedir.

Anahtar Kelimeler
Çiğneme, ortodonti, oklüzyon

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Introduction

Studies on mastication physiology and chewing patterns have a long history in dentistry. However, it has been observed that less studies were conducted on effect of chewing performance on malocclusion in the literature (1). Furthermore, there is no study found which compares the chewing patterns of young individuals with malocclusion who are about to complete normal occlusion development. Hypothetically, changes in chewing characteristics must be expected within the 6-month period from the onset of the treatment procedure because of changing of tooth movement. In this study chewing performance is measured and benchmarked before and after the study by using a jaw tracker device.

In the literature view, the following methods are commonly used in the studies investigating the chewing function (2): a-Analysis of chewing movements, b-Analysis of chewing muscle activity (Electromyography studies) (3-6) or c-Analysis of chewing process results (analysis of the status just after chewing and before swallowing a food particle) (1,7). Efficiency of restorations, the status before orthodontic studies, chewing analyses during and after the treatment process may provide important information about treatment process and outcomes (8). Thomas et al. (1) obtained the findings indicating that orthodontic treatment process may recover motor functions such as chewing in a pilot study conducted on 15 individuals.

No study has been found that focuses on the change of chewing patterns in the groups with orthodontic malocclusion on the individuals with class 1 occlusion and on the control group in the literature (9).

The chewing pattern is a periodical and functional movement style and aims to break down, mesh and prepare the food for digestion. All receptors in the system are enabled to create such function (3). A central pattern generator and associated motor neurons control strength, form, opening and closing durations and occlusion durations of biting forces and prevent damage of the organs in peripheral nervous system (10,11).

In a manuscript published by Hill (2), chewing cycle has three main components as follows; opening time (OT), closing time (CT) and occlusal time (OcT). Normal cycle duration varies between 600 and 900 miliseconds and each phase is roughly 1/3 of total chewing cycle. The OcT is slightly less than 1/3 of total chewing time. Record of chewing movements are observed at three planes as frontal, sagittal and horizontal. The most commonly used material used for chewing movements is the gum. Pattern of the chewing movement also depends on the food. Opening phase and closing phase were detected as 225±25 msec whereas occlual phase was 200±25 msec (10,12). The disoders during occlusal phase of teeth contacts of chewing phase would affect harmonization of the chewing system and cause pathological changes in the joints (13).

Analysis of temporomandibular joint (TMJ) under a load during functioning is important for operation for joint problems. Restructuring and recreation of TMJ with realistic anatomic and kinematic data is the only method providing an *in vivo*, three dimensional, dynamic and real time quantitative aspect to the relation between articulation surfaces of a joint (14).

It was revealed in a study conducted by Ngom P.I. et al. (15) where chewing efficiency was evaluated on 102 untreated individuals that recovery of chewing functions should be one of indication options as well as aesthetic and other indications for treatment. Yamashita et al. (16) reported in a review that a significant association exists between chewing efficiency and chewing pattern and hardness of the food was suggested to affect the chewing pattern and along with customization of the pattern, count may also be important.

Clark and Evans (17) have determined an ideal orthodontic occlusion frame where one of the basic rules was reported as demonstration of the function. However, Trawitzki et al. (14) could not detect any significant association between maximum isometric chewing strength and class 2 and class 3 dentofacial deformity in their study conducted on 125 volunteer patients. Furthermore, they reported that the values of both (class 2 and class 3) study groups were below the values of the control group. Effect of curve of spee on chewing efficiency was also investigated; it was concluded that the idea that a regular curve of Spee may create an efficient chewing is not true (17,18).

Therefore, the investigation of this topic is necessitated. The aim of the present study is to compare chewing patterns of the individuals with skeletally normal occlusion with those who have

abnormalities during an orthodontic treatment to offer an insight to further studies. In this comparison, differences of possible changes in chewing efficiency, opening and CT, OcT during chewing, vertical opening distance and the distance between opening and closing were analyzed.

Materials and Methods

The study protocol was approved by the Ethics Committee at the İstanbul Aydın University, Faculty of Dentistry, and written informed consent was obtained from all subjects prior to the study.

The present prospective clinical study was carried out on 63 individuals referred to Department of Orthodontics, Faculty of Dentistry, İstanbul Aydın University for treatment purposes in 2016 including 43 patients with malocclusion and average age of 16.8 years whose growth and development terminated partially and 20 individuals with normal occlusion and average age of 24.8 years who never had any orthodontic treatment before. Healthy individuals who were at permanent dentition period and might tolerate the treatment were also included into the study. The present research was divided into three groups.

1. Group 1; 25 individuals (58%) class 1, (8 male + 17 female)

2. Group 2; 18 individuals (41.9%) class 2, (9 male + 9 Female)

3. Control group including 20 class 1 individuals with normal occlusion who were not treated before.

Data collection was performed with the parameters consisting of three main components at two intervals: T0, before the treatment; T1 6th month after the treatment. A fixed Edgewise Roth technique was applied to the patient for treatment purposes. During first 6-month period of the treatment, 0.22-inch Roth bracket and 0.014 Ni-Ti arch wires for alignment of lower and upper mandible at the beginning were used; 0.016, 0.018 and 0.016x0.022 Ni-Ti arch wires were used during the treatment. The following criteria were considered during material collection;

1. Being at the end of pubertal excretion period skeletally,

2. Individuals being at permanent dentition period and eruption of all teeth,

3. Being angle class 1 and class 2 in terms of skeletal and dental molar association clinically and not having premolar and molar tooth loss more than one,

4. For the control group, having skeletal and dental molar and canine teeth with normal occlusion and angle class I and minimum crowding on the anterior zone. The following points are used to exempt patients from the study,

5. Individuals with previously known syndrome, systemic disorder, craniofacial abnormality, cleft lip/palate,

6. Individuals who had any orthodontic treatment before with removable or fixed apparatus,

7. Individuals with complaint of any periodontal and TMJ disorder,

8. Congenital tooth deficiency except 3rd large grinders.

Approval of İstanbul Aydın University, Medicine and Health Sciences Research Board and Commitee of Ethics were obtained to carry out the research (B.30.2.AYD.0.00.00-480.2/0106, EK-1) (ANNEX-1) 9) All individuals participated into the present research voluntarily and informed consent forms were obtained from all patients and their parents.

The study group (n=43) had average age of 16.8 years and Standard deviation of ±5.55 whereas the control group (n=20) had average age of 24.8 and Standard deviation of ±4.04.

The study materials consisted of lateral cephalometric and panaromic radiographs taken before and during fixed orthodontic treatment with/without extraction, intraoral and extraoral digital photos, orthodontic cast models and chewing analysis records (Figure 1).

Lateral cephalometric films of all participants were taken in İstanbul Aydın University, Department of Orthodontics. The anatomic spots and measurements used in the present research were obtained through selection from Steiner analyses. Ten lateral films were selected randomly and radiographs of same patients were drawn subsequently with 1-month interval to minimize the errors of drawing. Method error of each measurement was calculated to detect repeatibility. Measurement recurrence coefficients range between 0.95 and 0.99.

For the cephalometric points, planes and angles used in the research; point S was marked as Cella; point N was marked as frontonasal suture; point A was marked as subspinal and point B was marked as supramental points. Angles SNA, SNB and ANB were created according to Steiner's analysis.

Evaluation of lateral cephalometric films;

Films with angle ANB between > 0° and -<4° with crowding at lower and upper mandibles were selected as angle class 1 malocclusion group,

1. Films with angle ANB > 4° was evaluated as skeletal angle class 2 div1 and selected as class 2 malocclusion group.

2. Films with angle ANB between >0° and -<4° and individuals with normal occlusion who do not need any treatment were selected as the control group.

The association of chewing movements with occlusion and characteristics of chewing pattern of the present study were obtained by a device called Bio-JT developed by Bioresearch Inc. (Milwaukee, USA) and a chewing analysis sfotware developed by Prof. Maruyama (13,14). For occlusion evaluation of chewing movements in the study, head of the patient was positioned to make the frankfort plane paralel to the ground. The head part was placed to the patient for chewing movement and both sides were made symmetrical and even through right and left screws. The lower horizontal bar was placed; then, a special magnet adhesive which was specifically developed for the device was placed on anterior surface of lower-anterior teeth through a wax (Ormco, No.757-0001) and fixed. A gum was given to the participant and the participant was instructed to chew it on the left side. Same chewing movement was instructed to all participants both inthe control and study group and uniformity of the study was provided. After a chewing movement for about 15 to 20 minutes, record was completed and the procedure was ended, the records were kept in the computer for statistical analysis.

Analyses of the present study was performed on 7 parameters obtained through three main components during chewing: 1. Opening phase, 2. Closing phase, 3. Occlusal phase.

The software "Mastication" which operates as integrated in Biopak program with Bio-JT device was used (14). Chewing velocity was assessed and maximum opening distance during chewing was examined. The following parameters were analyzed through chewing pattern analysis; (1) Chewing OT, (2) Chewing CT, (3) Chewing OcT (4) Cycle Time (cycleT) (mm/sec), (5) Terminal Chewing Position (TCP) Vertical (mm) (vertical TP), (6) Opening Velocity (mm/sec), (7) Closing Velocity (mm/sec).

Statistical Analysis

Evaluation of all following findings provide data of chewing efficiency of the individuals in the study group without any orthodontic abnormality and the individuals with malocclusion. The statistical analysis performed with chewing analysis findings: Power and sample size calculation (Version: 3. 1. 2, Copyright 2017, Informer Technologies, Inc., New York, USA) software was used for selection of the individuals and creation of the groups. Although working with equal sample sizes are highly desired, the present study was carried out on the groups with equal unit sample counts and different unit sample counts. The study was started with 90 individuals and this sample count was reduced to 63 by considering the inclusion criteria. The strength of the test was accepted as 80% and significance level as ($p<0.05$) for hypotheses to be established on at least 13 patients (13 and 43 patients each in both groups) through sample calculation program (19).

All statistical analyses performed on the data base were done through SPSS software (IBM SPSS Statistics Version 19-22, New York, USA). Averages and standard deviations of all samples were calculated by this software. In consideration of equal sample counts ($n=n_1=n_2$) and different sample counts, "paired sample t-test" and nonparametric Wilcoxon test were used to compare two dependent group averages, and Mann-Whitney U test was utilized for comparison of two independent group averages. The p values of ($p<0.05$) and ($p<0.01$) were accepted as significant, respectively for the hypotheses to compare the differences between averages of the variables in both groups (20).

Results

In the present study, findings of the individuals who completed their development during the 6-month period of the treatment may be reviewed under three phases the first phase is the comparison of the statistical changes and the control of the importance to detect the differences between the control group and the group with initial malocclusion. Table 1 presents the comparison of the control group and malocclusion group under seven parameters, the values of the control group is lower than OcclT0 and CycleT0 changes and this was not statisically significant. The CT0 parameter was found higher, which

was not statistically significant. The measurement values of the other five parameters were found higher, and statistically significant changes are in question (p<0.01). The distribution of the variables of malocclusions according to the groups was provided in Figure 2.

Table 2 presents the association between initial values of the abnormality group and changes after the first 6-month treatment. Among such variables, OpenT0 (p<0.05) increased, and such increase is statistically significant. The increase at CT0, vertical TCP, Average opening velocity and Average closing velocity (p<0.01) levels is statistically significant. Furthermore, OcclT0 (p<0.05) decreased by treatment, and this was also found as statistically significant. Although the variable CycleT0 decreased by the treatment, such decrease was not statistically significant. Figure 3 provides the averages of the variables observed at the beginning and the end of the 6-month period.

Initial values of the individuals with class 1 and class 2 malocclusion were compared with the changes after 6-months through comparison of averages of two independent groups.

It was detected that class 1 and class 2 values of 6 variables increased by treatment and OcclT0 class 2 variable decreased; however, these were not found statistically significant.

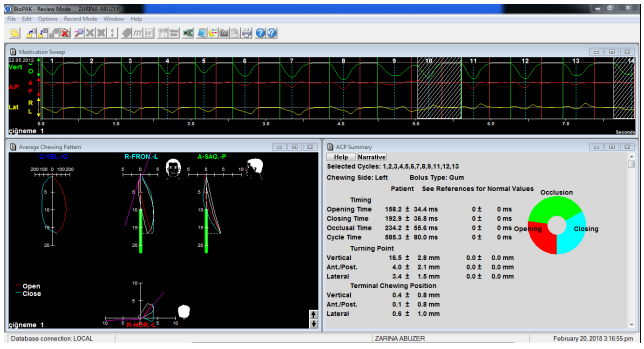

Figure 1. Evaluation of chewing patterns with JT

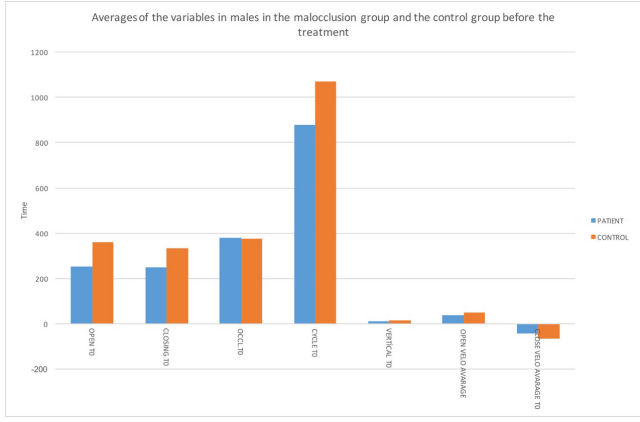

Figure 2. Averages of the variables of malocclusions before the treatment (T0: Control values) according to T0 group

Table 1. Averages of malocclusions before the treatment according to time 0; comparison with the control group and control of importance

Parameters	Mean	n	SD	SE	p	
Open time 0 (initial)	271.08	43	77.08	11.75	0.008	**
Open time 0 (control)	338.19	20	78.93	21.89		
Closing time 0 (initial)	258.66	43	50.08	7.67	0.006	**
Closing time 0 (control)	315.42	20	94.20	26.13		
Occlusal time 0 (initial)	384.07	43	173.11	26.40	0.786	NS
Occlusal time 0 (control)	370.13	20	112.24	31.24		
Cycle time 0 (initial)	864.965	43	277.12	42.26	0.773	NS
Cycle time 0 (control)	837.04	20	383.12	106.26		
Vertical TCP T0 (initial)	9.00	43	3.09	0.47	0	**
Vertical TCP T0 (control)	15.71	20	4.4	1.22		
Avarage open velo time 0 (initial)	34.54	43	14.64	2.23	0.001	**
Average open velo time 0 (control)	51.45	20	13.72	3.80		
Avarage close velo time 0 (initial)	-37.84	43	16.39	2.50	0.000	**
Average close velo time 0 (control)	-60.85	20	14.35	3.98		
(p<0.05)*, (p<0.01)**, NS: Not significant, SD: Standard deviation, SE: Standard error, TCP: Terminal chewing position						

Table 3 compares the changes of class 1 and class 2 malocclusion during at the and of the 6-month treatment period. Analyses of the dependent in-group averages of abnormalities were performed with paired t-test and Wilcoxon test. CycleT0 class 1, class 2 parameters and OpenT0 class 1 were not found as statistically signifcant. The other parameters showed changes with the treatment and statistically significant changes appeared after the treatment, ($p<0.05$) and ($p<0.01$). Table 4 includes the cephaloetric measurements.

Table 2. Changes of abnormalities and initial variables within 6-month treatment period and control of the associations

Parameters	Mean	n	SD	SE	p	
Open T0 (initial)	271.08	43	77.08	11.75	0.024	*
T1 (Treatment 6th Month)	307.70	43	74.83	11.41		
Closing T0 (initial)	258.66	43	50.08	7.64	0.002	**
T1 (Treatment 6th Month)	302.58	43	78.54	11.98		
Occlusal T0 (initial)	384.07	43	173.11	26.34	0.023	*
T1 (Treatment 6th Month)	312.44	43	91.27	13.92		
Cycle T0 (initial)	864.96	43	277.12	42.26	0.626	NS
T1 (Treatment 6th Month)	844.06	43	246.99	37.67		
TCP vertical T0 (initial)	9.00	43	3.10	0.47	0.000	**
T1 (Treatment 6th Month)	14.56	43	4.18	0.64		
Avarage open velo (initial)	34.58	43	14.64	2.23	0.000	**
T1 (Treatment 6th Month)	54.13	43	16.11	2.46		
Avarage close velo (initial)	-37.4	43	16.39	2.50	0.000	**
T1 (Treatment 6th Month)	-59.79		19.15	2.92		

($p<0.05$)*, ($p<0.01$)**, NS: Not significiant, SD: Standard deviation, SE: Standard error, TCP: Terminal chewing position

Table 3. Comparison of dependent in-group averages of the abnormalities

Parameters	n	Mean	SD	SE	p	
Open T0-T1	25	280.52	76.67	15.34	0.242	NS
Open T0-T1	18	257.96	77.86	18.35	0.046	*
Closing T0-T1	25	303.84	69.93	13.99	0.006	**
Closing T0-T1	18	313.06	82.92	19.54	.0.050	*
Occlusal T0-T1	25	253.94	50.38	10.07	0.021	*
Occlusal T0-T1	18	265.22	50.34	11.86	0.270	NS
Cycle T0-T1	25	287.63	54.20	10.84	0.307	NS
Cycle T0-T1	18	323.35	101.53	23.93	0.778	NS
TCP Vertical T0-T1	25	370.57	155.08	31.01	0.000	**
TCP Vertical T0-T1	18	402.81	198.61	46.81	0.000	**
Open velo T0-T1	25	53.35	12.85	2.57	0.000	**
Open velo T0-T1	18	55.22	20.15	4.75	0.002	**
Close velo T0-T1	25	-37.01	13.26	2.65	0.000	**
Close velo T0-T1	18	-38.98	20.33	4.79	0.004	**

T0: Initial, T1: the end of the 6-month period of the treatment, ($p<0.05$)*, $p<0.01$)**, NS: Not significant, SD: Standard deviation, SE: Standard error, TCP: Terminal chewing position, (25=class I, 18=class 2), paired t-test and wilcoxon test

Intergroup tests were conducted among the anomalies of the variables during the treatment period. Statistically significant changes did not occur.

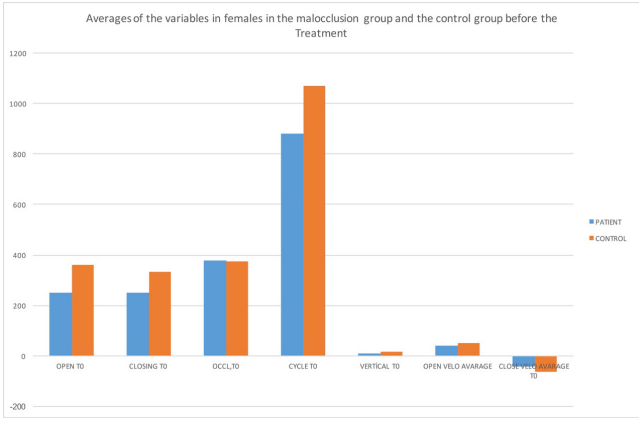

Figure 3. Averages of the variables at the beginning and the end of the 6-month period

Figure 4 demonstrates the average differences between initial and 6-months treatment values of class 1 and class 2.

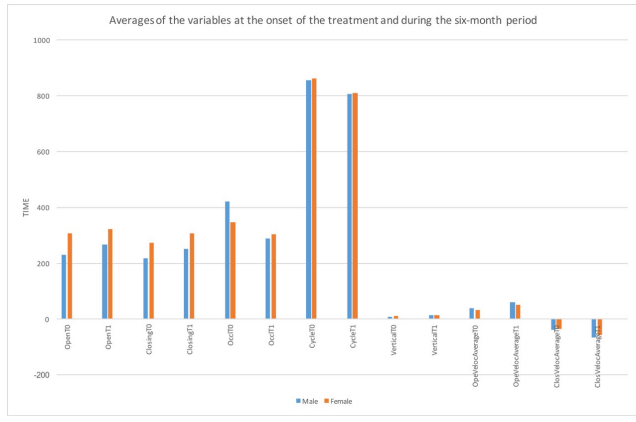

Figure 4. The average of the differences between groups of variables

Table 4. Cephalometric measurements

	n	Range	Minimum	Maximum	Mean		Standard deviation	Variance
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic
SNADERT0	43	10.3	73.00	83.3	798023.00	0.36	2.42	5.88
SNADERT1	43	10.70	72.9	83.6	79.75	0.38	2.52	6.35
SNADERT0	43	12.00	70.00	82.00	76.38	0.44	2.92	8.54
SNADERT1	43	12.00	67.00	82.00	76.73	0.45	2.98	8.92
SNADERT0	43	12.00	67.00	79.00	74.21	0.41	2.7	7.3
SNADERT1	43	12,00	67.00	79.00	74.47	0.43	2.83	8.04
ANDERT0	43	7.5	0.00	7.5	3.39	0.31	2.08	4.35
ANDERT1	43	7.7	0.00	7.7	3.03	0.3	1.97	3.92
PROGNBT0mm	43	6,00	-1.00	5.00	1.96	0.19	1.3	1.69
PROGNBT1mm	43	26.00	-1.00	25.00	2.6	0.57	3.73	13.98
GOGNSNT0der	43	24.00	20.00	44.00	33.33	0.76	5.03	25.35
GOGNSNT1der	43	22.4	21.6	44.00	33.49	0.8	5.24	27.53
COAT0mm	43	17.00	72.00	89.00	80.41	0.56	3.69	13.63
COAT1mm	43	17.00	72.00	89.00	80.82	0.59	3.91	15.36
ANPERPT0mm	43	12.00	-7.00	5.00	-0.61	0.35	2.32	5.42
ANPERPT1mm	43	12.00	-7.00	5.00	-0.36	0.3	2.00	4.01
ANSMET0mm	43	25.00	51.00	76.00	61.95	0.89	5.86	34.37
ANSMET1mm	43	24.00	52.00	76.00	62.62	0.84	5.52	30.51
BANPTMT0der	43	15.00	79.00	94.00	86.76	0.63	4.13	17.13
BANPTMT1der	43	13.00	80.00	93.00	86.75	0.57	3.79	14.37
SPpgoMeT0der	43	22.00	14.00	36.00	24.2	0.72	4.77	22.78

Table 4. contiuned

SPpgoMeT1der	43	23.00	13.00	36.00	24.72	0.72	4.72	22.3
PNPOGT0mm	43	21.00	-17.00	4.00	-5.74	0.59	3.88	15.1
PNPOGT1mm	43	20.00	-16.00	4.00	-5.24	0.54	3.57	12.8
WittsT0mm	43	12.00	-3.00	9.00	1.23	0.41	2.72	7.42
WittsT1mm	43	11.00	-3.00	8.00	0.87	0.4	2.63	6.95
NA1T0mm	43	17.00	0.00	17.00	5.08	0.45	2.95	8.76
NA1T1mm	43	17.00	0.00	17.00	5.11	0.41	2.74	7.52
NA1T0DRCE	43	33.00	6.00	39.00	22.63	1.16	7.66	58.69
NA1T1DRCE	43	26.00	13.00	39.00	23.52	0.79	5.21	27.14
NB1T0mm	43	9.00	0.00	9.00	4.43	0.31	2.02	4.1
NB1T1mm	43	9.00	0.00	9.00	4.86	0.28	1.87	3.49
NB1T0DRCE	43	23.5	11.5	35.00	24.74	0.84	5.5	3.02
NB1T1DRCE	43	17.3	15.7	33.00	25.69	0.66	4.29	18.46
T011DRCE	43	53.5	106.5	160.00	130.88	1.83	11.99	143.85
T111DRCE	43	52.5	107.5	160.00	129.35	1.32	8.64	74.58
ALT1APGT0mm	43	11.00	-3.00	8.00	1.69	0.3	1.98	3.93
ALT1APGT1mm	43	10.00	-2.00	8.00	2.04	0.29	1.91	3.66
U1AVERTT0mm	43	17.00	-5.00	12.00	3.62	0.53	3.51	12.38
U1AVERTT1mm	43	14.5	-3.00	11.5	3.91	0.44	2.88	8.33
OCCLSNT0	43	13.00	11.00	24.00	16.96	0.44	2.94	8.69
OCCLSNT1	43	23.00	2.5	25.8	16.53	0.57	3.75	14.07
IMPAT0DRCE	43	35.00	74.00	109.00	92.32	1.11	7.29	53.27
IMPAT1DRCE	43	36.5	74.5	111.00	93.2	1,00	6.6	43.58
HldawayfarkT0	43	10.00	-2.00	8.00	2.75	0.36	2.38	5.67
HldawayfarkT1	43	9.00	-1.00	8.00	3.02	0.35	2.33	5.46
S-LT0	43	21.00	34.00	55.00	45.46	0.67	4.43	19.68
S-LT1	43	22.00	34.00	56.00	45.83	0.73	4.81	23.17
S-ET0	43	8.00	15.00	23.00	19.32	0.3	1.98	3.93
S-ET1	43	7.5	15.00	22.5	19.31	0.27	1.82	3.34
OVERJETT0	43	9.00	1.00	10.00	4.01	0.32	2.12	4.5
OVERJETT1	43	6.6	0.4	7.00	3.38	0.26	1.73	2.99
OVERBITET0	43	10.5	-2.5	8.00	2.68	0.34	2.28	5.21
OVERBITET1	43	9.9	-2.9	7.00	2.45	0.28	1.89	3.6
6U6LOCPT0	43	8.00	-3.00	5.00	-0.43	0.24	1.57	2.47
6U6LOCPT1	43	8.6	-3.6	5.00	-0.34	0.26	1.71	2.94
3U3LOCPT0	43	8.6	-3.6	5.00	0.2	0.25	1.68	2.83
3U3LOCPT1	43	8.2	-3.2	5.00	0.59	0.27	1.79	3.23
ALT1-OCPT0	43	6.1	-0.4	5.7	2,00	0.21	1.42	2.02
ALT1-OCPT1	42	5.00	0.00	5.00	1.71	0.2	1.32	1.75
Valid N (listwise)	42							

Discussion

The chewing material used in the present study was the chewing gum. The quantity of the gum is equal at each chewing time and the hard gum is softened after 3 to 5 chewing cycles. All participants' chewing movements were recorded when the gum was hard and softened. The chewing patterns obtained in the control group of the present study was found consistent with those obtained by Kuwahara et al. (12,18). Furthermore, such data are quite similar when compared with the findings obtained by both Hill and Piancino et al. (2,21). Since the first 2 or 3 cycles of chewing were not recorded in the present study, this allowed the participants to adopt the equipment used. The results obtained by Papa Ibrahima Ngom et al. (15) are similar with the present study and harmonization of all organs in the chewing system was achieved.

A study conducted by Winocur et al. (22) evaluated the changes in the muscles after orthodontic treatments through the parameters of maximum biting strength, maximum sliding from intercuspal position and muscle sensitivity by palpation; and it was reported that neuromuscular modification just starts in orthodontic treatments and muscle adoptation is observed to be settled within 3-months after the treatment. Similarly, harmonization of opening and closing movements within first 6-months of the treatment is detected.

This necessary event for harmonization of neuromuscular mechanism was performed in a similar environment mentioned in Schindler's study (8). Comparison of opening and closing velocities between the occlusion group and the control group was used as an indicator for evaluation of chewing efficiency. The closing velocity of the present research was considered as the most important indicator of chewing technique as specified in the study of Radke. Radke reported in his study through use of JT that the velocity ratio in chewing velocity test is an important factor for evaluation of chewing efficiency (23).

Findings of the first phase in the present study are values of the control group as well as initial values of the treatment group. The significant difference between opening and CT fort the control group presented in table 1 is expected; the opening value of the individuals with malocclusion was 271.08 msec and this was very high in the control group as 338.19 msec. The difference between OpenT0 and OpenT1 was found significant in both groups ($p<0.01$). The difference between CT0 and CT1 was 56.763 msec which is significant ($p<0.01$). Opening period of the control group is 67 msec longer than OT of the malocclusion group. This significant difference is not an unexpected case for pre-treatment period. Higher value and significance of the difference are similar with findings of Lepley et al. (24) and Owens et al. (25). In a comparative study on chewing efficiency conducted by Lepley et al. (24), an artifical Cuttersil chewing material was chown by 30 individuals with class 1 occlusion and chewing performances were compared; they found the OT of the individuals without malocclusion as 274±22. When they evaluated with chewing efficiency, such time was detected to increase up to 325±27 msec in the individuals with malocclusion included into the poor chewing group and detected this difference as significant. The initial opening durations (338.20 msec) obtained in the present study are closely similar to durations of the individuals with malocclusion obtained in the study of J. Lepley (24). This indicated that chewing efficiency of the malocclusion group is lower and they have a less efficient chewing performance because of higher values than the control group. However, the difference between occlusion duration parameters in both groups was not significant; this result was considered that the malocclusion group acted faster and had a near-normal chewing pattern during closure. Total cycle time which was not significant at initial values is considered as a poor chewing pattern with a lower chewing performance. The most important parameters showing the chewing efficiency directly are Opening and Closing strength values and confirm this idea. Such results indicate that malocclusion group has a less chewing efficiency when compared with the control group. Values of the chewing efficiency increased due to some causes such as onset of the treatment for malocclusion, accurate movement of the teeth and resolvement of the crowding; in other words, malocclusion group showed a poor chewing efficiency. These findings may be seen in the values at months 6 of orthodontic treatment in Table 2. Since the occlusion started to improve, chewing opening and CT increased 34.54 msec than initial times and the difference was significant ($p<0.05$). Another important

effect of the treatment appeared on occlusion times; the initial value of Occlusion Contact Time was 384.07 msec and reduced to 312.44 msec ($p<0.05$). The most significant change at months 6 from onset of the treatment was increase of chewing efficiency (Initial value of Op-Velocity) which was 34.54 at the beginning to 54.13 (months 6 value of Op-Velocity) ($p<0.01$). This reveals the realistic change effect of the treatment on chewing efficiency.

Along with the increase in chewing efficiency in treated individuals, decrease in occlusal contact time indicates that a less time than before may be sufficient even occlusal contact zones were not changes. Occlusion time decreased and the OcclT0 value which has an initial value of 384.07 msec reduced to 312.44 msec ($p<0.05$). Functional occlusal zone was reported to have a more efficient chewing performance than the occlusal surface or plane surface. These findings comply with the outcomes of the studies conducted by Yawaka et al. (26), Owens et al. (25) and Okiyama et al. (27). The evaluation of the chewing movements of the individuals with class 1 and class 2 malocclusions whose growth and development were about to end at 6th month of the treatment suggested a statistically significant imporvement in the values obtained in both groups from onset of the treatment. Open-Velo T0-T1 values demonstrates the changes in initial and 6-months treatment values for class 2 are significant ($p<0.01$). However, the change rate in the group with class 2 malocclusion is more than the change rate of 25 individuals with class 1 malocclusion. Although such values are concrete, relative values obtained during comparison between them should not be evaluated as unexpected.

Conclusion

We observed the changes on chewing movements of the individuals with malocclusion whose growth and development are completed within such a short period of 6-months from onset of the treatment when compared with initial values as well as the individuals with normal closing. Such changes are dependent to the treatment. Although this rapid effect of the treatment is considered to appear by recovery of the occlusion, it may also appear due to disruption of routine chewing pattern with malocclusion which was settled into the memory. This should not be ignored at treatment phases. It is also important for undesired temporomandibular disorders after the treatment. Because, it should be considered that the changing occlusion relation may have a positive effect on TMJ. To monitor these studies at the end of the treatment and during retention period after the treatment would be useful.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee at the İstanbul Aydın University, Faculty of Dentistry.

Informed Consent: Written informed consent was obtained from all subjects prior to the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: There is no conflict of interest of this study.

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Original Article / Özgün Araştırma

Comparison of the Load-bearing Capacities of Monolithic PEEK, Zirconia and Hybrid Ceramic Molar Crowns

Monolitik PEEK, Zirkonyum ve Hibrit Seramik Molar Kronların Basma Dayanım Kapasitelerinin Karşılaştırılması

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Abstract

Objective: Although polyether ether ketone (PEEK) shows high biocompatibility in prosthetic dentistry, there is inadequate information about its clinical applications and limits. The purpose of this study was to compare the load-bearing capacities of PEEK, hybrid ceramic and zirconia crowns, which were fabricated using computer-aided design and computer-aided manufacturing (CAD/CAM).

Materials and Methods: Three groups (n=10) of high-resistance PEEK polymer, hybrid ceramic and zirconia were fabricated using CAD/CAM. A universal test machine was used to assume the fracture resistance of all specimens. The specimens were loaded until final fracture occurred and load at fracture was recorded. Fracture resistance data were statistically analyzed by Tukey honest significant difference multiple comparison test.

Results: There was no significant statistical difference between PEEK group (2214±236 N) and hybrid ceramic group (2325±264 N) in relation to the load-bearing capacities (p>0.05), while zirconia group (3292±192 N) showed the highest values for fracture load.

Conclusion: All three crown materials were successful against physiological occlusal forces. Regarding the limitations of this *in vitro* study, PEEK could be an alternative crown material for fixed dental prostheses.

Keywords
PEEK, hybrid ceramic, zirconia, crown

Anahtar Kelimeler
PEEK, hibrit seramik, zirkonyum, kron

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Öz

Amaç: Polieter eter ketonun (PEEK) protetik diş hekimliğinde göstermiş olduğu yüksek biyouyumluluğuna karşın, klinik uygulamaları ve sınırları hakkında yeterli bilgi bulunmamaktadır. Bu çalışmanın amacı, bilgisayar destekli tasarım ve bilgisayar destekli üretim (CAD/CAM) kullanılarak üretilen PEEK, hibrit seramik ve zirkonyum kronlarının basma dayanım kapasitelerini karşılaştırmaktır.

Gereç ve Yöntemler: Yüksek dirençli PEEK polimer, hibrit seramik ve zirkonyum olmak üzere üç grup (n=10) CAD/CAM kullanılarak üretildi. Tüm örneklerin kırılma direncinin değerlendirilmesi için üniversal test makinesi kullanıldı. Örneklere kırılma meydana gelene kadar yükleme yapıldı ve kırılma anındaki yük değerleri kaydedildi. Kırılma direnci verileri Tukey-honest significant difference çoklu karşılaştırma testi ile istatistiksel olarak analiz edildi.

Bulgular: Basma dayanım kapasitelerine göre PEEK grubu (2214±236 N) ile hibrit seramik grup (2325±264 N) arasında istatistiksel olarak anlamlı fark gözlenmezken (p>0,05), zirkonyum grubu (3292±192 N) kırılma dayanımında en yüksek değerleri gösterdi.

Sonuç: Her üç kron materyali de fizyolojik okluzal kuvvete karşı başarılıydı. Bu *in vitro* çalışmaların sınırları doğrultusunda, PEEK materyali sabit protezler için alternatif bir kron materyali olabilir.

Introduction

The main purpose of prosthetic dentistry is to use artificial materials to rehabilitate deficiencies in the teeth and oral tissues (1). For many years, metal-alloy crowns have been considered the gold standard in prosthetic dentistry. However, metal alloys have some limitations. For example, the aesthetics of these materials are limited by the metal framework and by the layer of opaque porcelain needed to mask the underlying grayish metal shade (2).

All-ceramic restorations are used as a standard in the aesthetic dentistry field due to their high aesthetic appeal, biocompatibility, and excellent mechanical properties, but they were later abandoned due to their low fracture resistance (3-5). The other framework structures, such as zirconia-based restorations, are the most commonly used due to their high strength, which reaches about 2000 MPa in fixed dental prostheses (FDPs) (6). When stabilized with Y_2O_3, zirconia offers the best properties for dental applications. However, due to the nature of metastability, zirconia-based restorations are susceptible to undesirable phase transformation at room temperature, which is known as "low temperature degradation" (7,8). This process may lead to yttrium loss, distort the stability of the tetragonal phase of zirconia-based restorations, and lead to uncontrolled tetragonal-monoclinic transformation (9). This creates surface roughness and microcracks, thus making water penetration possible. This ultimately leads to more phase transformation and consequently the mechanical loss of strength (7-10).

Any material used in prosthetic dentistry should produce satisfactory biocompatibility, aesthetic results, and mechanical properties for occlusal bites (11,12). In recent years, hybrid ceramics have been used in prosthetic dentistry due to their high biocompatibility (13). These materials, which feature the positive characteristics of both composites and ceramics, are produced to reduce abrasion from the opposite arch. This network structure of hybrid ceramics is formed by an interpenetration of ceramic and composite polymer networks; this is called a hybrid double network, and it mimics the interlocking of prism bands in natural teeth (14). The double-phase network structure of hybrid ceramics increases their fracture resistance and ensures both successful edge stability and an excellent marginal fit with oral tissues (15). The currently available member of this new hybrid ceramic group is GC Cerasmart (Cerasmart; GC America Inc, Alsip, IL, USA), which is a 71 wt% filled nanocomposite produced via computer-aided design and computer-aided manufacturing (CAD/CAM). The disadvantages of this material are that its resistance to flexibility is low and it is not as aesthetically pleasing as full ceramics are (15).

To overcome these existing problems, a new generation of composites has been proposed for prosthetic dentistry: elevated high-resistance polymers called polyether ether ketone (PEEK) (16). These highly resistant and high-performance thermoplastic polymers were first produced for industrial purposes in the 1980s and are members of the polyaryletherketone (PAEK) family, which comprises aromatic molecular chains of ether and ketone (16). The chemical structure of PEEK is similar to that of other polymers in the PAEK family. PEEK has high temperature resistance (up to 300 °C), high resistance to chemical abrasion, minimal radiation permeability, and the ability to be modified with various materials (such as carbon fibers and glass). Additionally, it can be used as an alternative to metal alloys (16-18). Due to its high biocompatibility, biostability, and radiosensitivity, along with its other mechanical properties, PEEK is an excellent alternative material for orthopedic and spinal implants (19). By the late 1990s, PEEK had emerged as the leading high-performance thermoplastic candidate for replacing metal implant components, especially in orthopedic and trauma applications (16). Today, PEEK is used in dentistry for applications such as dental implants, temporary implant abutments, removable prostheses, fixed partial dentures, implant healing caps, and implant-supported hybrid prostheses (20-22). Research has suggested that PEEK can be used to make crowns in prosthetic dentistry because the tensile strength of PEEK (80 MPa) is similar to those of dentin (104 MPa) and enamel (47.5 MPa). Thus, PEEK may have an advantage over alloy and ceramic restorations (17,18,23).

Although PEEK is a more aesthetic material than metal alloys are, it is not as transparent as hybrid ceramics are; another major disadvantage of PEEK is its low bonding strength with resin cement materials due to its low surface energy (20,24). It is difficult to

establish strong and resistant adhesion between PEEK and composite resin materials owing to PEEK's low surface energy and its strength to surface modification via chemical treatments (25).

In recent years, many studies have been carried out to improve PEEK's adhesive properties using conventional sanding, acid etching, and the plasma and laser roughening methods (20,25,26).

The aim of this *in vitro* study was to compare the load-bearing capacities of monolithic crowns made of zirconia, hybrid ceramics, and PEEK. The tested null hypothesis was twofold (1). The PEEK crowns would not demonstrate higher load-bearing capacities than the zirconia crowns did (2). There would be no significant difference between the hybrid ceramic and PEEK materials in terms of fracture resistance.

Materials and Methods

Crown Preparation

For the current study, a zirconia base model (Zirconia Pre Shaded Blank; Shenzhen Upcera Co, Shenzhen, Yuè, China) with a prepared primary maxillary right first molar was used as the basic cast. The anchor teeth presented an occlusal reduction of 2.0 mm, an axial reduction of 1.5 mm, and a chamfer with a convergence angle of 6 °C (Figure 1A). Specimens were fabricated using CAD/CAM and were divided into three groups featuring 10 specimens per group.

The materials used in the study included zirconia (Zirconia Pre Shaded Blank; Shenzhen Upcera Co, Shenzhen, Yuè, China), PEEK (PEEK Optima LT1, Invivo Biomaterial Solutions, Inc., Lancashire, England), and a hybrid ceramic (Cerasmart; GC America Inc, Alsip, IL, USA).

The digital impression technique is preferred for the production of crowns. The zirconia model was scanned using a CEREC 3 intraoral scanner (Cerec Omnicam; Sirona Dental Systems Inc. NY, USA). According to the manufacturer, no powder system needs to be applied to the zirconia model before scanning. The monolithic crown was designed on the computer to have thicknesses of 1.5 mm in the axial area and 2 mm in the occlusal area. The same CAD file was used for all crowns. The cement space was set at 30 µm. The complete CAM process for the 30 crowns was conducted using a three-axis milling machine (Yena D15; Turkuaz Inc, İzmir, Turkey). Zirconia frameworks were sintered at a temperature of 1500 °C to full density in a sintering furnace (Lava Furnace 200; 3M ESPE, St. Paul, MN, USA). However, for the PEEK and hybrid ceramic crowns, only the surface-polishing process was applied, not the sintering process (Figure 1B). The same parameters were loaded into the computer software for all specimens during the production process. Thus, the crowns made of all three materials had the same standards.

Load-Bearing Capacity

A universal testing device (Universal 3345 Testing Systems, Instrons, Inc., Norwood, MA, USA) was used to determine each crown's load-bearing capacity. The load was applied in the central fossa of the crown using a steel ball (diameter 5 mm) with a cross-head speed of 0.5 mm/minute. The specimens were loaded until final fracture occurred, and the load at fracture (N) was recorded (Figure 2).

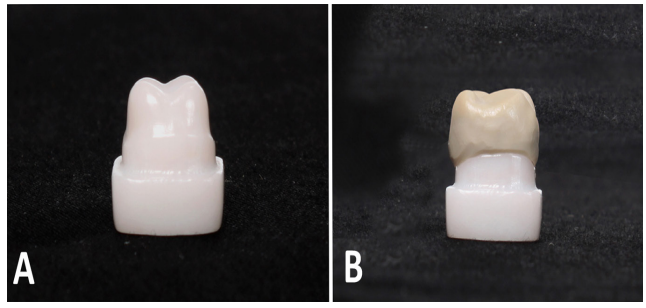

Figure 1. A) Photograph of a zirconia model, B) PEEK crown on zirconia abutments before fracture load measurement

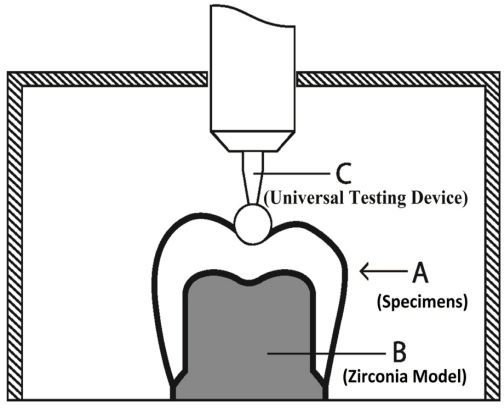

Figure 2. Schematic view of Load-bearing capacity tests. A) All specimens B) were fixed using the zirconia model and C) loaded on the central fossa of the frameworks along to the long axis using stainless steel rod with 5-mm diameter ball end

Statistical Analysis

Descriptive statistics (mean, standard deviation, minimum, median, maximum, and 95% confidence interval) were computed. Significant differences between the groups were tested with one-way ANOVA ($F=64.72$; $p<0.001$). For the data of all of the groups, Levene's test was used to verify the homogeneity of variances The Kolmogorov-Smirnov test was applied to the test data in a normal distribution within the groups. Tukey honest significant difference (HSD) tests were used to determine statistical significance. All of the statistical analyses were performed using R version 3.2.3 Copyright © 2015 The R Foundation for Statistical Computing free software. The level of significance was set at 5% ($p<0.05$).

Results

The load-bearing average, maximum and minimum values, standard errors and standard deviations for each group are shown in Table 1. The values obtained via the fracture loads (in newtons, N) were statistically compared using the Tukey-HSD multiple comparison procedure.

Table 1. Mean and range values for final failure force (newtons)

Zirconia	10	3292.82$^{(A)}$	192.78	60.96	3045.36	3565.32
Hybrid ceramic	10	2325.02$^{(B)}$	264.3	83.57	1985.35	2678.21
PEEK	10	2214.23$^{(B)}$	236.97	74.93	1932.86	2604.32

PEEK: Polyether ether ketone, (A, B): Represent a significant difference according to Tukey-honest significant difference test between the different fabricated crowns

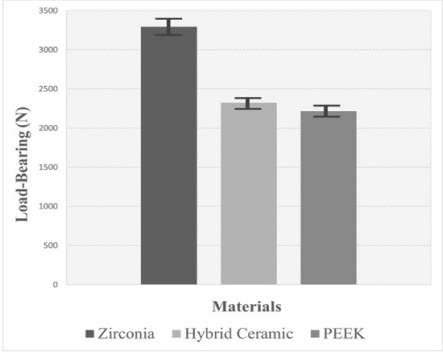

Figure 3. Bar graph for the fracture load of all three tested specimens groups

In terms of the fracture-resistance mean values, zirconia (3292.82 N±192.78 N, a characteristic fracture-load scale) was significantly higher than the others ($p<0.001$) were, but there was no significant difference between the hybrid ceramic (2325.02±264.3 N) and PEEK (2214.23±236.97 N) materials in terms of fracture resistance ($p=0.545$) (Figure 3).

Discussion

The purpose of this study was to evaluate the load-bearing capacities of PEEK, hybrid ceramic, and zirconia crowns fabricated using CAD/CAM. The data obtained in this study supported the null hypothesis. Many studies have investigated the maximum bite forces during mastication; in these studies, the mean maximum bite forces varied between 216 and 847 N; the highest bite force was in the first molar region: 807 N for men and 650 N for women (4,7,12). These values can increase to 965 N during the biting of an object (6). Therefore, it seems reasonable to assume that an initial fracture resistance of 1000 N would be required for a favorable clinical prognosis of the posterior region (7). In this study, the load-bearing values of all specimens exceeded 1000 N, so the load-bearing results showed that all groups had sufficient fracture strength against physiological occlusal forces.

As a result of continuous dental material research, PEEK can be engineered with a wide range of physical and mechanical applications. However, published peer-reviewed studies on PEEK's fracture resistance are scarce. Therefore, this *in vitro* test was performed, which included fracture load testing, to test PEEK's suitability as a material in the latter application. In addition, none of the published literature has compared the load-bearing capacities of PEEK, zirconia, and hybrid ceramic crowns.

In the present study, the CAD/CAM system was preferred, as it allowed for the use of high-quality materials, such as CAD/CAM-prefabricated blocks; this system also allowed for the standardization of manufactured crowns.

Alberto et al. (4) compared the load-bearing capacities of several ceramic materials using a three-point-bending test: two hybrids (Lava Ultimate and Vita Enamic), one feldspar (Mark 2), one lithium disilicate (IPS e-max), and one leucite-based material (IPS Empress). The study featured bars instead of crowns; the load-bearing capacities were found to

be 4400 N for the IPS e-max, 2600 N for the Lava ultimate, 2500 N for the Vita Enamic, 2300 N for the IPS Empress, and 2200 N for the Mark 2. The IPS e-max material had a statistically significantly higher capacity than the other materials did, but there was no statistically significant difference between the two hybrid materials. De Kok et al. (8) reported that the fracture load of a monolithic zirconia crown was higher than that of a hybrid ceramic crown. These results are comparable to those in the present study.

Stawarczyk et al. (22) investigated the load-bearing capacities and failure types for three PEEK FDPs fabricated using various techniques. CAD/CAM milled PEEK (2354 N) had a higher mean fracture load than did those pressed from granular PEEK material (1738 N) ($p<0.001$). CAD/CAM milled FDPs and those pressed from PEEK/C pellets each showed spontaneous and brittle fractures near the pontic, without the deformation of the FDP. However, some plastic deformation of the FDP occurred without fractures.

Taufall et al. (21) compared the fracture loads of various veneered PEEK three-unit FDPs. Digitally veneered FDPs (1882-2021 N) had significantly higher fracture loads than the remaining conventional veneering groups did (1008-1229 N) ($p<0.001$).

In another study, Stawarczyk et al. (20) reported that three-unit PEEK FDP copings experienced plastic deformation at 1200 N and fracture loading at 1378 N. In the presented results, which are parallel to the results of Stawarczyk et al. (20), the PEEK crowns showed plastic deformation without breaking completely. The presumed reason for this is that PEEK has a low Young's modulus (3-4 GPa) and great material compared with other conventional materials, such as zirconia (E-modulus 210 GPa) (27). The low level of the elastic modulus of PEEK material is thought to provide insufficient support and to generate more stress on the surrounding structure (28).

The load-bearing testing of new crown materials for FDPs can contribute to decisions on clinical applicability, thereby reducing the risks for participants the least in subsequent clinical trials. In this study, the load-bearing capacities of the samples were determined by using a universal testing device. However, the physiological tangential movement of the abutment teeth in the experiment has not been modeled, and therefore, the load bearing test allows for the comparison of various coating materials, but with limited clinical relevance. Despite load-bearing standardization, a different loading and wear condition can occur under clinical loading conditions.

A further limiting factor of the significance of this study is the fact that no cyclic and thermomechanical loading was used on the universal testing device. The only data obtained from a specially published non-peer-reviewed dental manufacturing report showed that there is some reduction in the relative fracture load after the fatigue test. However, such tests are beyond the scope of this initial applicability and screening study (22).

It has been suggested that test specimens should have the same critical defects as the crowns produced for clinical use and that environmental effects should be reflected in the laboratory settings (29). However, further research is required for longitudinal clinical aging data, or at least for trends, with additional aging through chewing simulation or thermal cycling.

Although dental hard tooth tissue has a lower elastic modulus than zirconia does, the base model made of zirconia does not reflect the actual strength distribution associated with crowns cemented on natural teeth. As the modulus of the elasticity of the abutment increases, the fracture resistance of the restoration increases (30). The cement may absorb the applied forces. This lack of cement might have created inferior bending forces and weakened the damping effect. In this study, the specimens were not cemented on the zirconia model. In addition, the possible effect of cement use on the load-bearing capacities of PEEK crowns should be tested in further studies.

Conclusion

Long-term investigations and advancements in PEEK fabricated using CAD/CAM processing are not still warranted. This study showed that the load-bearing capacity of PEEK was lower than that of zirconia and was similar to that of hybrid ceramic. All three crowns were successful against physiological occlusal forces, and in an *in vitro* study, it was concluded that PEEK could be an alternative crown material for FDPs. Despite the limitations of *in vitro* studies, this result is promising in that clinical conditions. However, it is necessary to investigate the mechanical resistance of these crowns under clinical loading conditions.

Ethics

Ethics Committee Approval: The ethics committee approval was not necessary since the study was *in vitro*.

Informed Consent: Externally and internally peer reviewed.

Peer-review: Externally peer-reviewed.

Author Contribution

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

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

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Original Article / Özgün Araştırma

Seropositivity of *Bartonella henselae* in Risky Human Population, Cats and Dogs

Kedi, Köpek ve Risk Grubu Insanlarda Bartonella Henselae Seropozitifliği

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Keywords
Bartonella henselae, risky human, cat, dog, seropositivity

Anahtar Kelimeler
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Abstract

Objective: *Bartonella* species cause several diseases in humans such as cat scratch disease, bacillary angiomatosis, peliosis hepatis, endocarditis, Carrion disease and trench fever. There have been cat scratch disease and bacillary angiomatosis cases reports in Turkey. The aim of this study is to determine the seropositivity against *Bartonella henselae* in cat/dog owners who are in the risk group, cats and dogs in Western Aegean region, Turkey.

Materials and Methods: In this study, *B. henselae* immunoglobulin (Ig) G positivity was investigated in a total of 281 samples including a total of 131 people, 34 of whom are pet cat/dog owners and 97 of whom are stray cat/dog owners; as well as a total of 105 cats, of which 57 pet cats, 48 shelter cats, and 45 pet dogs. Sera tested for the presence of antibodies against *B. henselae* IgG using immunofluorescence assay with two commercial kits.

Results: *B. henselae* seropositivity of pet owners was significantly higher than the stray cat/dog owners (26.5% vs 6.8%). B. henselae IgG was found positive in 36.2% of total cats, 22.8% of pet cats, 52.1% of shelter cats. *B. henselae* seropositivity was found statistically higher in shelter cats than pet cats. No positivity was detected in the samples taken from the dogs.

Conclusion: It is concluded that being pet owner at home poses a risk for *B. henselae*. For the differential diagnosis, especially in patients in close contact with cats, *B. henselae* infection should be considered.

Öz

Amaç: *Bartonella* türleri insanlarda kedi tırmığı hastalığı, basiller anjiomatozis, basiller peliozis, Carrion hastalığı, enfektif endokardit ve siper ateşi gibi pek çok hastalığa yol açmaktadır. Türkiye'de Bartonella'lara bağlı kedi tırmığı hastalığı ve basiller anjiomatozis olgu sunuları bulunmaktadır. Bu çalışmada, Türkiye'nin batısında, kedi/kopek sahibi riskli insan, kedi ve köpeklerdeki *Bartonella henselae* seropozitivitesinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya, 34'ü ev, 97'si sokak olmak üzere toplam 131 kedi/köpek sahibi ve 57'si ev kedisi, 48'i barınak kedisi olmak üzere toplam 105 kedi ile 45 ev köpeğinin serum örnekleri alınmıştır. Serum örneklerinde *B. henselae* IgG antikorları iki ticari kit kullanılarak immunfluoresan antikor yöntemi ile belirlenmiştir.

Bulgular: *B. henselae* seropozitifliği, ev kedi/köpek sahiplerinde sokak kedi/köpek sahiplerine göre (sırasıyla %26,5 ve %6,8). Seropozitiflik, istatistiksel olarak anlamlı

şekilde yüksek bulunmuştur. Kedilerde *B. henselae* seropozitifliği ortalama olarak %36,2 saptanmış olup, seropozitiflik barınak kedilerinde (%52,1) ev kedilerine (%22,8) göre istatistiksel olarak anlamlı oranda yüksek olarak belirlenmiştir. Köpeklerden alınan örneklerde herhangi bir seropozitiflik bulunmamıştır.
Sonuç: *B. henselae* için evde evcil hayvan sahibi olma risk oluşturmakta olup, özellikle kedilerle yakın temasta olan hastalarda, B. henselae enfeksiyonu ayırıcı tanıda düşünülmelidir.

Introduction

Bartonella genus received its name in 1909 from Alberto L. Barton who was working with and who also identified *Bartonella bacilliformis*, the cause of Carrion disease. *B. bacilliformis* has been accepted as the only member of this genus until a recent classification. *Bartonella* genus, which had previously been in Rickettsiales order, *Rickettsiaceae* family, was included in *Protobacteria* class, *Alphaproteobacteria* sub-group, *Bartonellaceae* family in 1993 (1). *Bartonella* species have adapted to many vertebrate hosts; humans, carnivores, rodents, ruminants, marine mammals, primates and bats. This group of bacteria has a high genetic diversity and adapt to changes in the ecological conditions. In recent years, new isolated species have been continually added to *Bartonella* genus (2). It is reported that seventeen of these species and 3 subspecies are associated with human disease; ([2] http://www.bacterio.net/bartonella.htm) (3-8).

All *Bartonella* species have specific mammalian hosts, in which they cause a long-lasting infection known as intraerythrocytic bacteraemia. Domestic cats are the principle reservoir for *B. henselae*, *B. clarridgeiae* and *B. koehlerae* (5,9,10). Among them, *B. henselae* is the most important zoonotic species to cause human disease.

B. henselae is continuously expanding and includes cat scratch disease (CSD), bacillary angiomatosis and peliosis hepatis, endocarditis, myocarditis, prolonged bacteremia and fever, ocular manifestations, encephalopathy, aseptic meningitis, acute hemiplegia, dementia, acute psychiatric symptoms, hepatosplenic abscesses, asymptomatic bacteremia, osteomyelitis, erythema nodosum, other skin lesions in human (11). Domestic cats represent the natural reservoir for the bacteria (12). Infected cats develop relapsing bacteremia, which may persist for up to two years (13,14). Cat flea (Ctenocephalides felis) transmits the bacteria from cats to new hosts. Although some of these animals may be bacteremic over a period of more than one year, cats have relatively asymptomatic infection (13). Transmission from cats to human mainly occurs by cat scratch or bite or possibly by flea bite.

According to the studies in humans, *B. henselae* immunoglobulin (Ig) G positivity is 8.7-19.8% in healthy children and adolescents, 10.3-28.9% in risky group humans, 11-16% in human immunodeficiency virus infected patient and 3.3-6% in blood donors (15-24). In Turkey, related to *Bartonella*, there are case reports of CSD and bacillar angiomatosis, and seroprevalence studies conducted in blood donors, cats and dogs samples (23,25-30). The objective of this study is to determine the prevalence of serum antibodies against *B. henselae* which has gained importance in recent years, in risky human, cats and dogs in Western Aegean region, Turkey.

Materials and Methods

This research was conducted by a team of researchers of Aydın Adnan Menderes University Veterinary and Medicine Faculties, Aydın, Turkey in blood samples collected from adults who are cat/dog owners, pet cats/dogs and shelter cats in Aydın and İzmir province. The permissions of both human and animal ethics committees were taken.

In this study, *B.henselae* IgG positivity was investigated in a total of 281 samples including a total of 131 people, 34 of whom are pet cat/dog owners and 97 of whom are stray cat/dog owners; as well as a total of 105 cats, of which 57 pet cats, 48 shelter cats, and 45 pet dogs. *Bartonella henselae* IgG antibodies were investigated in the all sera with indirect immunofluorescence antibody (IFA) method by using two commercial kits which were double compartmented *B. henselea &* quintana IFA IgG (Vircell, Granada, Spain) kits containing *B. henselea* cepa Houston-1 (ATCC 49882) and *B. quintana* (CIP 107 027 N) grown on Vero cells; and compartmented *Bartonella* IFA IgG (Focus, California, U.S.A) kits containing *B. henselea* and *B. quintana* bacteria

produced in yolk sac cells. Antibodies were investigated in cat samples by using fluorescein labeled goat anti-feline IgG as conjugate, and in dog samples by using fluorescein labeled rabbit anti-canine IgG (Santa Cruz Biotechnology, Texas, USA).

All sera samples were tested with *B. henselae & quintana* IFA IgG (Vircell) kits in 1/32 and 1/64 dilutions. The samples which were positive in 1/64 titers were consecutively tested with both kits in 1:64, 1:128, 1:256, 1:512 dilutions, and positive titrations were determined. Slides were viewed at a final magnification of 400× on fluorescent microscope by two different assigned researchers. Fluorescent intensity was graded as +1-+4, and the samples with fluorescence ≥+2 were considered as positive. Positive and negative controls were used for each study.

Results

B. henselae IgG positivity was on average 11.5% for risk group humans (cat/dog owners) (Table 1). *B. henselae* seroprevalence of pet owners was significantly higher than the stray cat/dog owners (26.5% vs 6.8%). *B. henselae* seropositivity was found in 36.2% of total cats, 22.8% of pet cats and 52.1% of shelter cats (Table 2). *B. henselae* seropositivity was found statistically higher in shelter cats than pet cats. The positivity in cats in 1/64 dilution was 20.0%, in 1/128 dilution was 13.3%, and in 1/256 dilution was 2.8% (Table 3). All dog samples were found negative for *B. henselae* IgG.

Table 1. *B. henselae* immunoglobulin G seroprevalence in cat/dog owners

Group	Number	*Bartonella henselae* immunoglobulin G positivity	
		Number	%
Pet cat/dog owners	34	9	26.5
Stray cat/dog owners	97	6	6.2
Total	131	15	11.5

Table 2. *Bartonella henselae* immunoglobulin G positivity in cats according to the groups

Group	Number	*Bartonella henselae* immunoglobulin G positivity	
		Number	%
Pet cats	57	13	22.8
Shelter cats	48	25	52.1
Total	105	38	36.2

Table 3. *B. henselae* immunoglobulin G positivity in cats according to the dilutions

Titer	*Bartonella henselae* immunoglobulin G positivity	
	Number	%
1/64	21	20.0
1/128	14	13.3
1/256	3	2.9
Total	38	36.2

The seropositivity of *B. quintana* IgG in some samples were found lower than *B. henselae* IgG titers and this was considered as cross reactivity (31).

Discussion

In this study, *B. henselae* seropositivity was determined in risk group human and both pet and stray cats in Western Aegean region of Turkey. *B. henselae* IgG positivity was 11.5% for risk group human (cat/dog owners), 26.5% for pet cat/dog owners and 6.2% for stray cat owners (Table 1). It was found that owning pet cats increases seropositivity significantly. Having a pet cat poses a higher risk to *B. henselae* infections than having a stray cat. In Turkey, related to *Bartonella*, there are case reports of CSD and bacillary angiomatosis (25-28). In a study conducted in Aydin province, Turkey, *Bartonell*a seroprevalence in blood donors was found 3,3% (24), and another study was conducted in Denizli, a neighbour city of Aydın, with blood donors *B. henselae* seroprevalence was found as 6.0% (23). The presence of similar seroprevalence rates on the two adjacent provinces suggests that *B henselae* infections are undergoing in this area. *Bartonella* spp seropositivity has been reported to be between 1.2% and 19.6% in healthy individuals and between 2.6% and 65% at different risk groups in various countries (32-35).

B. henselae seropositivity was found positive in 36.2% of total cats, 22.8% of pet cats and 52.1% of shelter cats. The seropositivity was lower in stray cat owners compared to pet cat owners. This result suggests that the seropositivity in humans may be associated with close contact to cats. Domesticated

cats are main reservoirs for *B. henselae* (9,36,37). Seroprevalence in cats varies according to geographical regions and climatic characteristics (18,38). *B. henselae* seroprevalence of domestic cats has been reported between 5 and 81% (36,38,39). In a similar study conducted in Ankara-Turkey, seroprevalence in cats was found as 18.8% (29). Seropositivity of *B. henselae* in cats is observed to be high in temperate and humid regions and low in cold and arid regions. This is due to the increased proliferation of cat fleas in temperate climates, so that in humid, temperate climates, cat fleas produce intensive infestation in the cats, resulting in the rise of *B. henselae* prevalence (36,38-40). Seropositivity against *Bartonella* species in humans is an expected outcome due to warm and mild climate of Aydın and İzmir provinces, where this study is conducted.

In dogs, *Bartonella* species may lead to clinical disorders such as endocarditis, bacillary angiomatosis, granulomatous hepatitis, lymphadenitis and granulomatous rhinitis (41-43). *B. vinsonii* subsp. *berkhoffii* is the first *Bartonella* type isolated from dogs, the isolation of *B.henselae, B. clarridgeiae* and other species has showed a significant increase (42). Although the role of dogs for transmission of *Bartonella* species is unclear, they are important due to the possibility that they may become reservoirs. In two studies conducted in the US, *B. henselea* seropositivity have been reported in 10.1% of healthy dogs and 27.2-32% of the ill dogs (44,45). In another study conducted in Spain, *B. henselea* seropositivity was found as 16.8%, whereas *B. vinsonii* subsp. *berkhoffii* was found as 1.1% (46). In our study, all pet dogs samples were negative in *B. henselae* IgG. This result may be related to the fact that the study was conducted in pet dogs, and in order to suggest that *B. henselae* is not present in dogs in our region, it is necessary to conduct a research on both stray and shelter dogs. There has been no study on *B. henselae* isolation in neither pet nor stray/shelter dogs in Turkey. However, in a study all species which has been isolated was *B. vinsonii* subsp. *berkhoffii and B. vinsonii* subsp. *berkhoffii* IgG seroprevalence has been reported as 3% in stray dogs and 12% in rural dogs (30).

Study Limitation

The limitations of this study include several topics since it was not possible to distinguish individuals as stray cat/dog owners. Moreover, since the maintainance of contact, sampling, disease anamnesis and screening of stray cats and dogs were difficult, the use of these animal samples were limited in this research. The recent *Bartonella* infection could not be diagnosed because *Bartonella* IgM did not be investigated in the sera samples.

Conclusion

In humans, CSD is usually clinically suspected and diagnosed by the determination of antibodies against *B. henselae* or the bacterial DNA from the tissue kept. Since it is difficult to culture *Bartonella* species from human samples, serological diagnosis is the first step to confirm the preliminary diagnosis. Many tests have been developed for the serological diagnosis with varying in sensitivity and specificity (IFA, enzim immünoassay, immunoblot). Indirect IFA is one of the most commonly used methods of serological tests. IgG titer is 1/512 and above in CSD. However, low antibody titers, such as 1/64 and 1/128 titers, can be found in both patients and healthy controls. As low antibody titers can be found at the beginning or the end of disease, they also can only be related to the exposure to the causative agent (18,47). Two different commercial kits were used in this study. First, all sera were run in 1/64 dilution with *B. henselae* & *quintana* IFA IgG (Vircell) kit. The sera which were subsequently positive were also studied with the *Bartonella* IFA IgG (Focus) kit. The difference between these two kits is that the wells on the slides of the screening kits contain *B. henselae*, cepa Houston-1 (ATCC49882) and *B.quintana* (N CIP 1070271) bacteria produced in Vero cells, while the other kit contains bacteria-infected Vero cells. As the production methods of the kits differ, there are also differences in terms of cost. Direct and dilution results were found to be compatible between the kits used in this study. Regnery and colleagues used Vero cells infected with *B. henselae* as antigens in CSD serology (48). Many researchers have used *B. henseale* and infected Vero cells as IFA antigens based on the work of Regnery and colleagues (20,21,49,50)

Bartonella species cause many different types of clinical findings in human and animals. Especially the role of cats spreading CSD to people by being reservoirs is well known. Isolation of *Bartonella* species, which are increasingly important zoonotics, in cats and dogs in a geographical region may be a sign

of humans in that having the disease, and therefore epidemiological studies in human and animals are required. This study is the first report of the *B. henselae* positivity seroprositivity in cats, dogs and pet owners in Western Aegean region of Turkey. We found out that being pet owner at home poses a risk for *B.henselae*. Especially in patients in close contact with cats, *B. henselae* infection should be considered for the differential diagnosis.

Ethics

Ethics Committee Approval: HEK/2008/006, EK/2008/00224.

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Not made Concept: N.A., B.K., S.K., M.T., M.E., Design: N.A., M.E., S. K., B.K., M.T., Data Collection or Processing: S.K., U.P., S.T., B.K., M.E., A.M.A., Analysis or Interpretation: N.A., B.K., S.K., M.E., A.M.A., M.T., Literature Search: N.A., B.K., M.E., S.K., A.M.A., Writing: N.A., B.K., M.E., S.K.

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Original Article / Özgün Araştırma

Investigation of Potential Genotoxic Effects of Magnetic Field Used in Imaging

Görüntülemede Kullanılan Manyetik Alanın Genotoksik Etkileri

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Abstract

Objective: Although the high magnetic field is commonly accepted as harmless for biological tissues, there is no consensus about its biological effects. This study aims to investigate probable genetic damages of magnetic field on biological tissues using a simple and widely accepted method, Allium test.

Materials and Methods: The same sized healthy Allium cepa (onion) plants were exposed to 0.5 Tesla magnetic field for 0, 8, 24 and 72 hours as groups of four. Allium test was applied and at least 4.000 cells were counted for each group. Observed chromosomal aberrations were analyzed and photographed.

Results: Magnetic field application adversely affected the mitotic activity in the experiment group compared to the control. The chromosomal aberrations increased in proportion to increased magnetic field exposure times. The most encountered aberrations were C-metaphase, stickiness, lagging chromosome, anaphase bridge, micronucleus, irregular anaphase, and polar deviation. The group comparisons showed statistically significant differences between the control group and 8, 24 and 72 hour magnetic field exposure groups.

Conclusion: This study has shown potential genotoxic and mutagenic effects of high magnetic field on Allium cepa root tip cells using Allium test. Although there is a need for more studies, the data in the study show that the strong magnetic field leads to chromosomal disorders.

Keywords
Magnetic field, metaphase, mutagenic effects, Allium test, *Allium cepa*

Öz

Amaç: Yüksek manyetik alan yaygın olarak biyolojik dokular için zararsız kabul edilse de, biyolojik etkileri konusunda fikir birliği yoktur. Bu çalışma, basit ve yaygın olarak kabul gören Allium testini kullanarak biyolojik dokulardaki manyetik alanın muhtemel genetik hasarlarını araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Aynı büyüklükte sağlıklı Allium cepa (soğan) bitkileri 0, 8, 24, 72 saat 0,5 Tesla manyetik alana maruz bırakılan dört grupta incelendi. Maruziyet sonrası Allium testi yapılmış ve her grup için en az 4.000 hücre incelenmiştir. Bu hücrelerde gözlemlenen kromozom anormallikleri analiz edildi ve fotoğraflandı.

Bulgular: Manyetik alan uygulaması, mitotik aktiviteyi olumsuz etkiledi. Kromozomal sapmalar, manyetik alana maruz kalma sürelerine oranla arttı. En sık görülen sapmalar C-metafaz, yapışkanlık (stickiness), geri kalmış kromozom (lagging chromosome), anafaz köprüsü (anaphase bridge), mikronükleus (micronucleus), düzensiz anafaz (irregular anaphase) ve kutup sapması (polar deviation) oldu. Grup

Anahtar Kelimeler
Manyetik alan, metafaz, mutajenik etkiler, Allium testi, *Allium cepa*

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karşılaştırmaları, kontrol grubu (0 saat) ile 8, 24 ve 72 saatlik manyetik alan maruziyet grupları arasında istatistiksel olarak anlamlı farklılıklar gösterdi.
Sonuç: Bu çalışma, Allium testini kullanarak güçlü manyetik alanın potansiyel genotoksik ve mutajenik etkilerini göstermiştir. Her ne kadar daha fazla çalışmaya ihtiyaç bulunsa da, bu çalışmadaki veriler göstermiştir ki, güçlü manyetik alan kromozomal bozukluklara yol açmaktadır.

Introduction

Living organisms are continuously exposed to magnetic fields at different doses in our modern world. The use of devices generating high magnetic fields in industrial processes, medical diagnostics, new vehicles for transportation and some research facilities is expected to expand significantly in the near future.

In the last years, there has been a substantial increase in human exposure to strong static magnetic fields, especially after the usage of magnetic resonance (MR) technology as a clinical method for imaging. With MR, a high static magnetic field has become a standard for imaging in the health sector. Today most of the MR systems are applied in 0.2 to 3.0 Tesla ranges and their use for imaging is becoming more and more widespread.

According to the U.S. Food and Drug Administration, static magnetic fields up to 8.0 Tesla which is used in clinical MR system, is considered harmless to humans. Accordingly, numerous MR procedures are being performed on all age groups, including pregnant women and newborns. However, many researchers found that the safety and the potential effects associated with MR systems and procedures are still under debate (1-3). Due to the frequent use of high magnetic field and the controversial reports about the effects of static magnetic field, this study aims to investigate the potential genotoxic effects that might be produced by static magnetic field, using Allium cepa test.

A magnetic field is generated by magnetic materials or electrical currents. The geomagnetic field (the magnetic field of Earth) is due to its solid iron core and it is not constant. It varies at the surface from 26 micro-tesla (μT) from the equator to about 60 μT to the poles. Magnetic fields can be also produced artificially by medical imaging systems, power lines, electromagnets and everything that carries electric current. Due to the wide use of artificial magnetic fields, the level of magnetic fields exposure to humans may be considerably increased over the last century.

In Magnetic Resonance Imaging (MRI) field, different types of electromagnetic fields are used: 1. The static magnetic field used in this study, which aligns the axes of the proton, and creates a magnetization vector in the physical body, 2. The radio-frequency electromagnetic wave, centered at the proton resonant frequency and 3. The gradient magnetic field, producing different resonant frequencies for aligned protons that means different slices of the body will resonate at different frequencies contingent on their spacial positions on the axes; these gradient magnetic fields permit spacial localization of bi-dimensional MRI slices and so the reconstruction of three-dimensional MRI images (1-3).

This study used the Allium cepa test to identify the biological effects of MR. This test is accepted as a practical and sensitive method to detect environmental genotoxic and mutagens (4). This test is also enables to demonstrate the effects on DNA of the exposed organisms for various chemicals or other tested agents on DNA. The Allium cepa test has good correlativity compared with other test systems, such as mammalian test systems and also it is very sensitive. Actually, it has been accepted as a standard test to determine chromosomal damages affected by environmental and chemical agents (4). One study showed 82% of correlation for Allium cepa test in relation to the carcinogenicity test in rodents showing that Allium cepa test was virtually the same as the one observed for mammalian test systems (5). The Allium cepa test was found to be more sensitive than the Ames and the Microscreen tests (4). In addition, another study reported that the Allium cepa test system is one of the best-constituted test systems to evaluate the potential of genotoxicity (6). Thus, it is suggested that Allium cepa test is a good alternative to screen genotoxic potential of environmental chemicals.

Materials and Methods

We did not use any sample belongs to humans or animals in our study. For this reason ethics committee aproval or informed constent was not necessary.

Preparation of Allium Cepa Materials

Healthy bulbs of Allium cepa (onion) (4n=20) that were about the same size, were chosen. One control group (n=5) and 3 exposed groups (n=3x5) were placed on a plate. The onions were kept away from moisture and direct sunlight exposure. The outer shells of the bulbs were carefully peeled. Rooting was done in an incubator at 25±2 °C temperature without light. The control group was kept in the same conditions without any exposure to magnetic field.

Magnetic Field Exposure of Allium Cepa Materials

Allium cepa plants were placed at the back of the MR bore on a table in platters as is shown in Figure 1 with a red cross and then exposed to 0.5 tesla magnetic field (Philips Achieva 1.5 T). The strength of the magnetic field was measured with a specific device called Teslameter (Metrolab, presicion NMR Teslametre PT 2025, Switzerland) (Figure 2). The intensity of magnetic field was confirmed to be 0.5 T at 112 mm of Z axis in the central bore (Figure 1). Then the three groups of onions were kept in that location for 8, 24, and 72 hours.

Rooting of Allium Cepa Materials

Following the magnetic exposure, onions were placed into small tubes filled with tap water for rooting in an incubator set at 25±2 °C temperature without light. The control group was rooted under the same conditions without any exposure to magnetic field. Each group consisted of five onions.

Chromosomal Analysis

The roots were cut when they reached a length of 1.5-2.0 cm and were fixed for 24 hours at +40 °C within freshly prepared ethyl alcohol and glacial acetic acid (3:1) mixture. The roots were then washed with 70% ethyl alcohol and kept in a refrigerator immersed in 70% alcohol. Roots were hydrolyzed with 1N HCl (2-3 minutes) before examination and then stained with acetoorcein for 3-4 hours. Examination slides were prepared according to the squash method (7) and chromosomes examined under the microscope (Olympus BX51). Allium test was applied and at least 4.000 cell nuclei were examined for each group. The scorings were done in a blind way. The chromosomal aberrations were counted in each nucleus and some of them photographed (Figure 3).

Statistical Analysis

The statistical analyses were performed by scoring the dividing cells. Both mitotic index and chromosomal aberrations were analyzed. To determine the significance among mean values, One-Way ANOVA was used. The variance was normal.

Results

Examination of slides has shown that magnetic field exposure adversely affected mitotic activity compared to the control group. However, this effect was not found to be statistically significant between groups (p>0.05) (Table 1).

Chromosomal aberrations during mitosis following exposure of Allium cepa root tip cells to magnetic field was given in Figure 3. Chromosomal aberrations increased in proportion to the in-creased time of magnetic field exposure. The most frequently encountered aberrations were C-metaphase stickiness, anaphase bridges, lagging chromosomes, fragments and polar deviations (Figure 3).

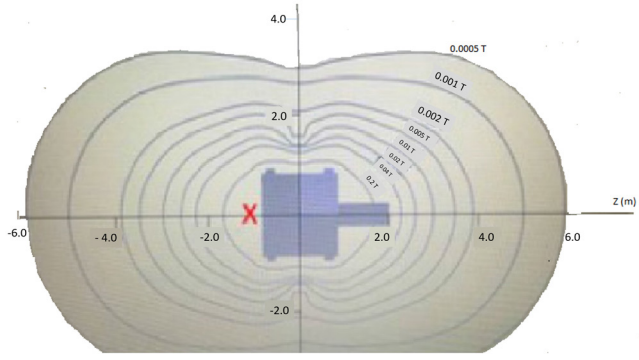

Figure 1. The placement of the plants within the magnetic room is marked as red x on a Gauss map. The magnet is shown in the center, the magnetic field strength decreased gradually with the square function of distance as indicated by Gauss lines

Figure 2. A Tesla-meter used for the measurement of strength of location shown in Figure 1

Table 1. The genetic analyses results of the control and 0.5 Tesla magnetic field exposed groups (8, 24 and 72 hours) of Allium cepa roots

Exposure Groups	ETC	Proph	Metaph	Anaph	Teloph	TM	MI	TA	TA(%)*
Control	4880	57	35	46	41	179	3.66	25	0.51*
8 hours	5920	26	23	48	48	145	2.44	80	1.35*
24 hours	4612	66	58	48	52	224	4.85	117	2.53*
72 hours	4560	54	41	43	43	181	3.96	117	2.56

ETC: Examined total cell, Proph: Prophase of cell cycle, Metaph: Metaphase of cell cycle, Anaph: Anaphase of cell cycle, Teloph: Telophase of cell cycle, TM: Total mitosis, MI: Mitotic index, TA: Total Aberrant Cells, *The differences between the ones marked with different letters were statistically significant (p< 0.05), The significance was determined by one-way ANOVA test

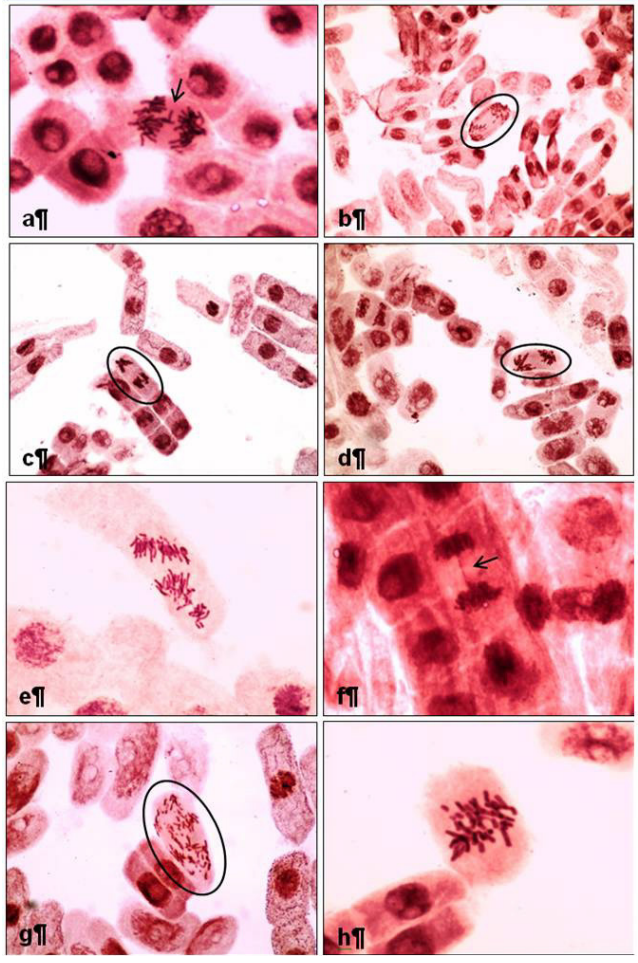

Figure 3. Different types of aberrations induced by static magnetic field in Allium cepa root-tips after 8, 24 and 72 hours static magnetic field exposures. The pictures were visualized with light microscopy at 1000x magnification. a) lagging chromosome, b) irregular anaphase, c) stickiness, d) polar deviation, e) multipolarity, f) anaphase bridge, g) fragment, h) C-mitosis

Table 2. Comparison of the total aberrant cells of exposure groups with each other and the resultant statistical significance levels

ANOVA statistical test results for exposure groups comparisons		
Groups		**p**
Control	8th hour	0.003 *
	24th hour	<0.001 *
	72th hour	<0.001 *
8th hour	24th hour	0.044 *
	72th hour	0.044 *
24th hour	72th hour	1.000

The significance was tested by one-way ANOVA test, *The difference was statistically significant (p<0.05)

Comparing groups that were exposed to magnetic field 24 and 72 hours to 8 hours have shown that as the time of magnetic field exposure increased, aberrations were encountered more frequently. The groups were compared using one-way ANOVA test. The percentages of total aberrations were significantly different between the control group and 8, 24 and 72 hours magnetic field exposure groups (p<0.05). However, there was no significant difference when 24 and 72 hours exposure groups were compared (p>0.05). The statistical significance values are presented in Table 2.

Discussion

Our study showed that static magnetic field brings about potential genotoxic effects on Allium cepa

plant. Many chromosomal aberrations pointing to the presence of chromosomal breakage were seen in common Allium cepa exposed to a magnetic field when compared to the control. All these findings reveal that static magnetic field especially within the first 24 hours, result in chromosomal breakage and mitotic anomalies.

Although it was shown that magnetic field causes root elongation (8), little is known about its genotoxic effect. These studies usually employed low electromagnetic fields (9). In these studies, low-intensity magnetic field found in high voltage electric lines was shown to increase mitotic activity and chromosomal anomalies.

There were studies showing static magnetic field interaction with free radicals causing genetic mutations, supporting our findings (10). However, these studies point out the difficulty in demonstrating the biological effect of static magnetic field (3). Because Allium test method is accepted as a practical, fast, simple and easy method (11), we preferred this valid method to show the effect of magnetic field on biological tissues. This method has been used to evaluate DNA damages, such as chromosome aberrations and disturbances in the mitotic cycle (12). The causes of chromosomal aberrations had collected in three groups (13). In the first group, we see mitotic chromosomal aberrations such as C-mitosis, multipolarity, polyploidy and lagging chromosome due to the interaction of chemical substances with mitotic apparatus as spindle and aster fibers. The second group comprises chromosomal stickiness as the result of a physiological effect on chromosomes during division. Chromosomal breakage, chromosomal bridges, fragments, and micronucleus can be mentioned in the third group. C-mitosis was one of the aberrations observed in all three magnetic exposure times. C-mitosis is the cell phase where chromosomes are irregularly distributed in the metaphase. The employed magnetic field might have caused a disturbance in spindle fibers similar to colchicine. As a result, centromere division lags and chromosomes are paired (replicated) but could not separate from one another and are irregularly distributed within the cell. Such abnormalities in the metaphase could result in a decrease of mitotic index. C-mitosis has been encountered in many tests where physical and chemical agents were used (14,15,16). These aberrations in metaphase may lead to a decrease in mitotic index. C-mitosis has been observed in many test materials exposed to various physical and chemical stresses. Another aberration we encountered was anaphase bridges. Chromosomal bridges are often the result of clastogenic effect from use of environmental and chemical agents or sticking of chromosomes in metaphase causing chromosomal breaking and fusion of chromosome and chromatids (17). Irregular inversion and translocation of chromosomal segments may also lead to chromosomal bridges (18). Chromosome bridges or inter-chromatid connections, are fibers that hold sister chromatids together until late anaphase or telophase. In other words, chromosomes could not be separated easily at anaphase because of these bridges. This abnormal state causes genomic instability. Sometimes, when connections become too stretched, chromatids might break at or near the centromeres (19). This breakage may occur at different points in both sister chromatids resulting in chromosome like bodies called fragments.

It is accepted that static magnetic fields smaller than 1 T are not genotoxic (20,21). However, Suzuki et al. (22) found that micronucleus (a chromosome or a fragment of a chromosome that is not integrated by one of the daughter cell nuclei during cell division) frequency in mice were increased significantly in a dose dependent manner, when the mice exposed 2, 3, or 4.7 T static magnetic fields for 24, 48, or 72 h. Micronucleus frequency was significantly increased after 4.7 T and 3 T but there was no significant effect after 2 T exposure. Therefore, the study showed that higher magnetic fields may have induced directly or indirectly chromosome separation during cell division.

The mitotic index of the exposure groups differed from that of the control group according to the exposed magnetic field. Mitotic index was observed decrease to 2.44 in 8 hour exposure group compared to the control group, which had a mitotic index of 3.66. Although mitotic index in 24 and 72 hours exposure groups increased to 4.85 and 3.96 respectively, the difference was not statistically significant (Table 1).

The decrease observed in the mitotic index could be attributed to mitotic inhibition. Various physical and chemical factors could lead to disturbances in cellular loops. Fitzgerald and Brehaut (23) have proposed that the decrease in the mitotic index could be a result of inhibition of DNA synthesis. Van't Hof has pointed out

that blockage or prolongation of the G2 phase of cell cycle delays or prevents the cell to enter mitosis (24).

Although further studies are needed in cell cultures, mammals, and human tissue, the present study shows the effects of static magnetic field on cell division and chromosomes in Alium cepa plants. Revealing the relationship between magnetic field and plant responses may lead to further studies on mammals to explain how and why these chromosomal aberrations may occur. Despite numerous investigations, the connection between a magnetic field and cancer or any other diseases is not clear. However, from the past and present studies, it seems that exposure to prolonged static magnetic field may be capable of producing chromosome aberration. The reasons of increased number of chromosome aberrations may be thought to results from the damages in DNA in interphase caused by free radicals to defects in the processing of the signals because of the magnetic field.

Study Limitation

The biochemical differences between plants and mammals.

Conclusion

It seems that, in this study and the literature, magnetic field may affect living organisms negatively. Therefore, long exposure time of magnetic field must be avoided. There are studies reporting the systemic effects of the static magnetic field. For example, Ghodbane and colleagues (25) showed that the static magnetic field of 128mT, 1 hour/day induced apoptosis in rat liver and increased liver catalase activity. Abdelmelek et al. (26) showed that noradrenergic systems in rat's gastrocnemius muscles were affected and HSP72 levels were increased. Another study showed that static magnetic field had a possible effect on blood through enzymes release and the blood cell proliferation (27). Observing adverse effects of high magnetic field on chromosomes makes one think whether this physical effect has any adverse effects on other living organisms, besides the target tissue. Therefore, more research is required to adequately understand the mechanisms associated with the static magnetic field used for imaging purposes.

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Ethics

Ethics Committee Approval: It was not necessary.

Informed Constent: It was not necessary.

Peer-rewiev: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.Ö, S.K, Design: S.K., Y.Ö., Data Collection or Processing: S.K., M.Ö., B.D., B.S., Analysis or Interpretation: S.K., M.Ö., Literature Search: H.K., Y.Ö., Writing: H.K., Y.Ö.

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Original Article / Özgün Araştırma

Rational Use of Drugs Among Inpatients and Its Association with Health Literacy

Hastalarda Akılcı İlaç Kullanımı ve Sağlık Okuryazarlığı ile İlişkisi

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Abstract

Objective: Rational use of drugs (RUD) plays a vital role in the success of the treatment process. Considering that use of medicines is also related with decision making mechanisms of individuals, RUD and health literacy levels should be considered together. The aim of this study is to determine the attitudes of patients related to RUD and its relationship with health literacy.

Materials and Methods: This cross-sectional analytical study was conducted on 361 patients hospitalized at a University Hospital carried out in Turkey. A rational usage of drug questionnaire and The Turkish health literacy survey questionnaire was used.

Results: It was found that 60.7% of patients kept leftover drugs to use later. Self medications with antibiotics were 32.6%; regular vitamin intake was 31.7%. From a total of 361 patients %56.2 of them reported that they stopped their medications when they felt better. The majority of the patients had insufficient/problematic health literacy level. Informing physicians about previously used medications/health problems, informing healthcare professionals about food/drug allergies; use of medications for the adequate period of time, consulting to a physician when a side effect occurs, using drugs with physicians' recommendation increase, as health literacy level increases.

Conclusion: Improving health literacy level of the public can reduce self-medication, improve adherence to therapy and so increase awareness of RUD.

Keywords
Medication adherence, self medication, health literacy, Turkey

Anahtar Kelimeler
Tedaviye uyum, kendi kendine tedavi, sağlık okuryazarlığı, Türkiye

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Öz

Amaç: Akılcı ilaç kullanımı (AİK) tedavi sürecinin başarısında yaşamsal bir rol oynar. İlaç kullanımının, bireylerin karar verme mekanizmaları ile ilişkisi olduğu düşünüldüğünde, AİK ve sağlık okuryazarlığı düzeylerinin birlikte değerlendirilmesi gerekmektedir. Bu çalışmanın amacı hastaların akılcı ilaç kullanım ile ilişkili tutumlarını ve bunun sağlık okuryazarlığı ile ilişkisini değerlendirmektir.

Gereç ve Yöntemler: Bu kesitsel tipteki çalışma Türkiye'de bir üniversite hastanesinde yatan 361 hasta üzerinde gerçekleştirilmiştir. Akılcı ilaç kullanım anketi ile Türkiye sağlık okuryazarlığı araştırması anketi kullanılmıştır.

Bulgular: Hastaların %60,7'si daha sonra kullanmak üzere ilaçları saklamaktadır. Antibiyotiklerle kendi kendine tedavi %32,6; düzenli vitamin alımı %31,7'dir. Üç yüz altmış bir hastadan %56,2'si kendilerini iyi hissettiklerinde tedavilerini sonlandırdıklarını belirtmiştir. Hastaların çoğunun yetersiz/problemli düzeyde sağlık okuryazarlığı düzeyi vardır. Daha önce kullanılan tedaviler/sağlık sorunları konusunda hekimleri bilgilendirme durumu, sağlık personelini gıda/ilaç allerjileri konusunda bilgilendirme, verilen tedavilere yeterli süre devam etme, herhangi bir yan etki olduğunda hekime danışma, hekimlerin önerileri doğrultusunda ilaç kullanma durumları, bireylerin sağlık okuryazarlığı düzeyi arttıkça artmaktadır.
Sonuç: Halkın sağlık okuryazarlığı düzeyinin geliştirilmesi, kendi kendine tedaviyi azaltır, tedavilere uyumu artırır ve dolayısı ile AİK ile ilgili farkındalığı artırır.

Introduction

In 1985, during the conference of experts on rational use of drugs (RUD) in Nairobi, held by the World Health Organization (WHO), RUD was defined as; "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community" (1). Prescription of incorrect, unnecessary medications or medications that are not in compliance with essential drugs list or updated guidelines and use of high priced medicines cause many problems in varying degrees worldwide (2,3). WHO estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them correctly (4). From an individual point of view, habits for medication use are affected by physicians' recommendations of as well as the individual's socio-demographic and social status (5).

Prescription indicators, patient treatment indicators and healthcare unit indicators can be used to measure RUD (6). Additionally, most of the studies on RUD reviewed analysis of prescriptions and channels through which patients supply their medicines. Although irRUD is a major problem in developing countries, limited number of studies were found describing reasons for RUD (7-9).

Although Turkey is one of the first countries to have an infrastructure for RUD, many local and nationwide studies have found that the public is not sufficiently informed about RUD and does not follow RUD principles (10,11). When a person gets sick, he/she can use the already available drugs at home based on their previous experience with similar symptoms or ask drugs from friends or directly buy from the pharmacy and use such drugs in doses and time periods different from those that a physician would recommend (5,10,12,13). Such approaches can lead to serious medical consequences.

In addition to socio-cultural, economic and regulatory mechanisms, RUD is closely related with education and health literacy level. Health literacy can be defined as, "individual's knowledge, motivation and competence to access, understand, appraise and apply information to prevent disease and promote health in daily life" (14). Low health literacy is shown to have a negative effect on patient adherence to medical treatment and management of diseases, lead to insufficient knowledge about diseases, and thus, is associated with higher hospitalization, morbidity and premature death (15). At this point, RUD and health literacy should be considered together. Decision makers can use RUD rates as an evaluation criteria to determine the effectiveness of the actions improving the health literacy levels. The aim of this study is to determine the habits of patients related to RUD and its relationship with health literacy.

Materials and Methods

This cross-sectional study was conducted on patients who were hospitalized at Aydın Adnan Menderes University Hospital between 7-14 September 2015. The Hospital is in the western Turkey with 533 beds. For the inclusion criteria of the study, participants who were 18 years and older and had stable conditions related with their health status were included. When intensive care patients, pediatric service patients and patients in isolation were excluded, 361 patients met the inclusion criterias and all target population was reached. Ethical approval was obtained from Ethical Committe of Aydın Adnan Menderes University (2015/645).

A semi-structured questionnaire form was used to collect data from patients by face-to-face interviews. The questionnaire form consisted of three major sections: 1) Demographics 2) RUD questionnaire 3) Turkish health literacy survey questionnaire (TSOY-32).

Demographic questionnaire included questions about patients' age, sex, education, job, type of residence and income level. RUD questionnaire was developed by the Turkish Medicines and Medical Devices Agency for inpatients and consisted of 29 questions. The questions are about storage conditions for drugs, leftover/unused drugs, decisions to use drugs, side effects, information sources and etc.

TSOY-32 was developed by a Turkish consortium (2016) consisting of academicians and specialists from the Turkish Ministry of Health. Its conceptual framework was based on The European Health Literacy Survey Questionnaire (Q47). Crohnbach's alfa level of the scale was 0.927. It is a 4 point likert type questionnaire with responses ranging from very easy (1) to very difficult (4). The lowest score is 32 and the highest is 128. Total scores are standardized to be in between 0 and 50. Four levels of health literacy was defined as; 0-25 for "inadequate", >25-33 for "problematic", >33-42 for "sufficient" and >42-50 for "excellent" as in the European Survey (16).

The data was analysed with software of SPSS 17.0 version. Normality distribution of continuous data was analysed with histogram and the Kolmogorov-Smirnov test. After examining the normality of distributions of the responses, descriptive statistics were presented as means ± standard deviation (minimum-maximum) for continuous variables and as percentages for the categorical variables. In order to make comparisons between RUD and health literacy levels (because levels of health literacy is an ordinal type variable), chi-square test for trend was used. Type-1 error (α) level was assumed as "0.05".

Results

The mean age of the patients was 48.2±16.7 (18-87) years and 52.5% of them were female; 55.9% had an educational level of primary school or less; 19% had university degrees.

Regarding the habits of patients for medication use; 60.7% of the patients reported that they kept leftover drugs at home to use later, 31.2% had 6 or more packages of medications at home, 43.4% reported that they could dispose medications without even opening the package. Only half of the patients kept drugs in a cool and dry place at room temperature. On the other hand 68.0% of them stored drugs that require cold chain storage, on refrigerator door bins.

In case of using a leftover drug at home, 91.5% of the patients reported that they checked whether the drug was appropriate for their health problems. Only 45.5% of them declaired that they consulted to a physician while using them. One forth of the patients reported that they could request for prescription medications without being sick such as; analgesics (62.3%), antibiotics (10.4%), flu drugs (9.4%), vitamins (2.8%), medications for stomach problems (2.8%), eye drops (1.9%) and others (allergy drugs etc). On the other hand, almost half of the patients (44.5%) reported that they might not buy their prescribed drugs. From 361 patients, 20.8% of them reported that they could get medical advices from relatives/friends and 23.6% of them said that they could give drug recommendations to individuals with similar complaints.

The majority of the patients (85.1%) declaired that they visited a physician when they felt sick but 56.2% reported that they stopped their medications when they felt better. From 361 patients, self medication with antibiotics were 32.6%, regular vitamin intake were 31.7%; and adverticed medicinal drug intake were 14.2%. Furthermore 59.8% of the participants believed that injectable medications were more effective.

Most of the patients (79.7%) gave "physicians/prospectuses" as their sources of information for medications and only 47.2% reported that they were informed about which food could be taken with the drugs they used. 71.6% of the patients reported that they informed healthcare personnel about their food/drug allergies and 86.1% informed about their previous medications/healthcare problems before their medical examinations. Distribution of some of the parameters of RUD were given in Table 1.

Regarding the definition and frequency of reading the prospectuses; 42.3% of the patients gave a correct definition and only one third of them (35.7%) reported that they "always" read prospectuses. From 361 patients, 30.9% of them expressed their wish to get an education on RUD.

Health literacy levels of the participants were as following; 48.6% was insufficient, 36.5% was problematic, 10.4% was sufficient and 4.5% was excellent. In most of the parameters related with RUD in this study, appropriate habits were seen with the increasing level of health literacy.

Table 1. Distribution of some of the parameters of rational use of drugs		
RUD questionnaire	**n**	**%**
Consumin leftover drugs from previous treatments		
Keeping them for further use as necessary	216	60.7
Giving them to a healthcare institution	140	39.3
Unused or leftover drugs at home		
None or 1-5 packages**	245	68.8
6 packages and over	111	31.2
Number of disposed unopened packages of medications that are expired		
None**	201	56.6
At least one box	154	43.4
Storage place of drugs for which no storage condition is specified		
At room temperature, in a clean and dry place**	186	52.2
Fridge/freezer/deep freeze	170	47.8
Storage place of drugs for which cold chain management is specified		
Refrigerator door bin**	114	32.0
Fridge/freezer/deep freeze	242	68.0
Considerations when using leftover/unused drugs available at home		
Looking for the appropriateness to illness/expiration date**	325	91.5
Pay no attention	30	8.5
Source of information in case of a leftover drug had been using at home		
Physician**	162	45.5
Person other than physicians	194	54.5
Requesting prescription drugs without being sick		
Yes	90	25.4
No**	264	74.6
Requesting prescription of drugs based on recommendations of relatives/friends		
Yes	74	20.8
No**	281	79.2
Not buying drugs from pharmacies although they were prescribed		
I do not	155	44.5
I do*	193	55.5
First person to consult for health problems		
Physician**	303	85.1
Other	53	14.9
Recommending drugs to people who have similar complaints		
Yes	84	23.6
No**	272	76.4
Informing the physician about previously used medications/health problems		
Yes**	286	86.1
No	46	13.9
The period in which prescribed drugs are taken		
For the recommended period**	156	43.8

Table 1. continued

Until symptoms subside	200	56.2
Self medication with antibiotics for flu-like symptoms		
No**	240	67.4
Yes	116	32.6
Regular use of vitamin/mineral supplements		
Yes	113	31.7
No**	243	68.3
Sources of information for medication use and side effects		
Physician/prospectuses**	283	79.7
Relatives/friends etc.	72	20.3
Consulting to a physician when a drug has caused side effects		
Yes**	271	76.1
No	85	23.9
Use of advertised medical products for treatment		
No or after consulting to a physician**	302	85.8
Yes	50	14.2
Informing healthcare professional about any food or dug allergies		
Yes**	255	71.6
No	101	28.4
Taking drugs without any medical examination		
Yes	124	34.9
No**	231	65.1

RUD: Rational use of drugs, *percentage of the column, Answers marked with **refer to positive attitudes about rational use of drugs

Table 2. Distribution of some of the parameters of rational use of drugs according to health literacy levels

RUD questionnaire	Health literacy levels*					
	Insufficient	Problematic	Sufficient	Excellent	χ2	p
Consumin leftover drugs from previous treatments						
Keeping them for further use as necessary	59.5	63.1	62.2	50.0	0.014	0.906
Giving them to a healthcare institution	40.5	36.9	37.8	50.0		
Unused or leftover drugs at home						
None or 1-5 packages**	68.2	69.2	73.0	62.5	0.006	0.937
6 packages and over	31.8	30.8	27.0	37.5		
Number of disposed unopened packages of medications that are expired						
None**	53.2	60.5	56.8	62.5	1.036	0.309
At least one box	46.8	39.5	43.2	37.5		
Storage place of drugs for which no storage condition is specified						
At room temperature, in a clean and dry place**	46.8	54.6	73.0	43.8	3.372	0.066
Fridge/freezer/deep freeze	53.2	45.4	27.0	56.3		
Storage place of drugs for which cold chain management is specified						
Refrigerator door bin**	37.0	27.7	29.7	18.8	3.528	0.066

Table 2. continued

Fridge/freezer/deep freeze	63.0	72.3	70.3	81.3		
Considerations when using leftover/unused drugs available at home						
Looking for the appropriateness to illness/ expiration date**	89.6	93.0	97.3	87.5	3.135	0.333
Pay no attention	10.4	7.0	2.7	12.5		
Source of information in case of a leftover drug had been using at home						
Physician**	44.5	44.6	48.6	56.3	0.661	0.416
Person other than physicians	55.5	55.4	51.4	43.8		
Requesting prescription drugs without being sick						
Yes	27.7	24.6	22.9	12.5	1.793	0.181
No**	72.3	75.4	77.1	87.5		
Requesting prescription of drugs based on recommendations of relatives/friends						
Yes	27.7	16.3	10.8	6.3	10.248	0.001
No**	72.3	83.7	89.2	93.8		
Not buying drugs from pharmacies although they were prescribed						
I do not	52.7	55.8	56.8	80.0	2.664	0.103
I do*	47.3	44.2	43.2	20.0		
First person to consult for health problems						
Physician**	82.7	85.4	91.9	93.8	2.926	0.087
Other	17.3	14.6	8.1	6.3		
Recommending drugs to people who have similar complaints						
Yes	23.1	26.2	18.9	18.8	1.151	0.711
No**	76.9	73.8	81.1	81.3		
Informing the physician about previously used medications/ health problems						
Yes**	80.5	88.5	97.3	93.3	8.176	0.004
No	19.5	11.1	2.7	6.7		
The period in which prescribed drugs are taken						
For the recommended period**	35.3	47.7	51.4	87.5	16.575	<0.001
Until symptoms subside	64.7	52.3	48.6	12.5		
Self medication with antibiotics for flu-like symptoms						
No**	64.2	70.0	67.6	81.3	1.905	0.167
Yes	35.8	30.0	32.4	18.8		
Regular use of vitamin/mineral supplements						
Yes	39.3	20.8	40.5	18.8	3.697	0.055
No**	60.7	79.2	59.5	81.3		
Sources of information for medication use and side effects						
Physician/prospectuses**	75.7	81.4	91.9	81.3	5.347	0.058
Relatives/friends etc.	24.3	18.6	8.1	18.8		
Consulting to a physician when a drug has caused side effects						
Yes**	68.2	80.0	91.9	93.8	14.266	<0.001
No	31.8	20.0	8.1	6.3		

Table 2. continued

Use of advertised medical products for treatment						
No or after consulting to a physician**	77.9	93.0	91.7	100.0	13.875	<0.001
Yes	22.1	7.0	8.3	-		
Informing healthcare professional about any food or drug allergies						
Yes**	63.6	75.4	86.5	93.8	14.139	<0.001
No	36.4	24.6	13.5	6.3		
Taking drugs without any medical examination						
Yes	32.0	38.5	43.2	18.8	4.341	0.689
No**	68.0	61.5	56.8	81.3		
RUD: Rational use of drugs, *percentage of the column, Answers marked with ** refer to positive attitudes about rational use of drugs						

Statistically significant parameters were as; requiring prescriptions advised by relatives/friends, using of advertised medicinal products without prescription, informing the physician about the medications being used or health problems/allergies; compliance to period of time while using drugs and consulting to a physician when a side effect occured. With the increasing level of health literacy, requesting prescription of drugs based on recommendation of relatives/friends and using products advertised in the media decreased. Informing physicians about previously used medications/health problems, informing healthcare professionals about food/drug allergies; use of medications for the adequate period of time, consulting to a physician when a side effect occurs, increase as health literacy level increases ($p<0.05$). Distribution of some of the parameters of RUD according to health literacy levels was given in Table 2.

Discussion

RUD is related with patients, physicians, medicine supply systems under the control of the healthcare industry, regulations, lack of knowledge about drugs and a combination of all these factors. Due to ageing of societies worldwide, use of medicines is expected to increase more in coming decades leading to an excessive burden on them. This increase in medication use compels people to increase their health literacy level i.e. while using medicine correctly and improving their decision making skills. Therefore RUD and health literacy should be considered together and play an important role when developing relevant policies. This study specifically focused on patients' RUD and found that irRUD was an important problem and it was related with health literacy.

Regarding medication use habits of the patients, more than half of them (60.7%) reported that they kept leftover drugs at home and almost half of them declaired that they sometimes had to discard medications without even opening them. A study conducted by Göçgeldi et al. (13) in Ankara reported similar results as keeping leftover drugs at home 50.0%. In another study conducted in the same city, 61.2% of the study population reported that they kept leftover drugs at home, 26.8% reported that they disposed them as home waste, 11.2% reported that they gave them to relatives/friends, and 9.6% reported that they gave such drugs to the community clinics (17). In a study conducted in Malaysia, 9.1% of the participants reported that they gave leftover antibiotics to other family members when they got sick (18). The results of these studies show that people tend to keep leftover drugs at home and have inappropriate habits for the disposal.

Regarding storage of the drugs that should be stored at room temperature, more than half of the participants stored their drugs in appropriate conditions however this percentage drops to 30% when it comes to drugs that require a cold chain. A study conducted by Ilhan et al. (5) reported that most of unused drugs (60%) were stored in fridges. It is very important that drugs should be stored as instructed as recommended by the physician in order to maintain their mechanisms of action. Otherwise it

should be remembered that drugs can cause harmfull effects instead of curing diseases.

Bilgili et al (17) reported that in case of using leftover drugs at home, 43.2% of study participants reported that they paid attention to expiration dates; 31.1% of them checked whether the drug was suitable for their condition, 8% checked that the package was intact and 1.8% reported they paid attention to none of the above. In another study from Turkey declaired that the percentage of people checking the expiration date was 80.2% (14), and in the Malaysian study this was 92.2% (18). In our study the percentage of patients who reported that they did not check anything was 8.5%, findings of other responces were similar. In case of using a leftover drug at home, 45.5% of our study group reported that they would consult to a physician, whereas this rate was 72.8% in a study conducted in Ankara (17). Reasons for this difference can be the fact that our study sampling consisted of inpatients, were using medication frequently, were presenting to healthcare institutions more often and therefore had more tendency to self-medication.

25.4% of the patients in our study reported that they could request drugs without being sick and the three most common prescribed drugs were analgesics (62.3%); antibiotics (10.4%) and flu drugs (9.4%). In a study conducted in Malaysia, it was found as 15% (19). İlhan et al. (5) reported that the percentage of people who kept medications at home was 78.6% and 40% of such medications were analgesics, 19% were flu drugs, 15% were for stomach problems and 14% were antibiotics. The percentage of people who use drugs without consulting to a physician was 76.4% in Manisa and 71.5% in Ankara and most of these drugs were analgesics which is similar to our study (7,14). In a study conducted in adolescents in Brazil, self medication was found to be 52.6% (19). In our study the percentage of participants who regularly took vitamin and mineral supplements was 31.7% whereas in a study conducted in Yemen it was found to be 11.2% (7). The reason why this percentage was higher can be explained as vitamin and mineral supplements are sold as over the counter products both in pharmacies and other stores in Turkey and people tend to use such supplements without any recommendation from physicians.

In our study, 20.8% of the patients reported that they could have prescriptions based on recommendations of relatives/friends. This rate was 45% in Ankara (5). Different study groups might explain the differences in results.

As in many developing countries, irrational use of antibiotics is also an important problem in Turkey. 32.6% of the patients in our study reported that they used self-medication with antibiotics for flu-like symptoms. Nayir et al. (11) reported that the rate of self-medication was 58.9% and self administered antibiotics was 29.4% in Elazığ, Turkey. Self medication with antibiotics was reported as 70% from senior university students in Ghana (20), and in a Malaysian study, antibiotics used without consulting to a physician for flu-like symptoms was 7.6%. However 47% of the individuals reported that they could request antibiotic prescription from physicians for such a condition (18). In a study conducted in Trinidad and Tobago 20% of the participants obtained antibiotics drugs without prescription (21). In a Palestine study, 85.9% of participants thought that borrowing and using antibiotics from relatives/friends was not a good behavior and 67.7% thought that taking antibiotics without prescription was incorrect (22). In countries where access to medications is relatively easy and sales of medications without prescription is possible drugs are not used rationally. At this point, regulatory authorities should develop and implement necessary regulations and make regular controls to determine whether such regulations are complied with and use enforcement as necessary. Many studies on RUD indicate to a widespread misunderstanding and misuse of drugs among consumers, distributor and physicians (10,11,18). One of the inappropriate habit is to stop using medications when complaints are resolved. In a study conducted in Malaysia 37% of the participants reported that they stopped using antibiotics when their complaints were resolved (18) and in our study this percentage was 56.2%. In the Palestine study, one third of the participants reported that they could stop taking antibiotics when they felt better, in a study conducted in senior university students who could be described as a higher group of class in the society in Ghana, use of antibiotics for adequate period was found as 54% (20,22).

Both in this study and in various studies in the literature the most frequently used information sources about drugs are physicians and other healthcare professionals (5,22). It is important to

explain medical information in a clear, understandable language until it is fully understood. But another thing which is as important as this, is to have a sufficient level of health literacy. Although healthcare consumers receive the treatments recommended by healthcare professions, the factor which determines medication use eventually, is the decision making mechanisms of individuals (5). This study found that as the health literacy level increases, some parameters of RUD also increase. Requesting prescription for drugs without a physician's recommendation decreases as the level of health literacy increases and informing physician about personal health condition and consulting to a physician when a side effect occurs increase with the increasing level of health literacy. Many studies indicate that there is a relationship between the health literacy level and medication/treatment adherence and that as health literacy level rises, the frequency of use of healthcare services and hospitalization decreases (15,23,24). Health literacy has been reported to be very important for patient safety and would reduce errors in medication use and improve adherence to therapy and affect access/use of health information (25). It is important that healthcare professionals use a clearer and more easily understandable language when providing health information to people with low level of health literacy and provide guidance for safe information sources. Since the study population consists of inpatients, they are in an older age group with higher risk conditions and with higher medication requirements. Healthcare institutions for inpatients should be used as a good opportunity to educate the society on RUD as the patients stay for longer periods in the hospital until their treatments are completed.

No relationship was found between some parameters of RUD such as using leftover drugs, storage in appropriate conditions, requesting prescription from physicians without being sick, making recommendation on medications to relatives/friends, self medication with antibiotics/vitamin supplements- and health literacy levels. In developing countries such as Turkey, cultural characteristics, previous experiences and common beliefs in the society can play a more effective role in such behaviour patterns.

Conclusion

The awareness for RUD is not sufficient in the study group. National campaigns are needed through the collaboration of professional groups such as medical and pharmaceutical organizations, international organizations, governments, non-governmental organizations, universities, educational institutions and the media sector to increase awareness on RUD. Additionally, improving patients' health literacy can reduce self-medication and improve adherence to therapy and therefore unnecessary and incorrect treatment processes can be avoided.

Strengths and Limitations

The strength of the present study is that it is the first study evaluating the relationship between RUD and health literacy in Turkey. Several limitations should be as, study carried out among hospitalized patients that the results can not be extrapolated to general population. This population constitutes a segment of the society that is highly more inclined to information about health. Thus the results might be better than the general. Another limitation might be memory factors that affect the responses.

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Ethics

Ethical Committee Approval : Ethical approval was obtained from Ethical Committe of Adnan Menderes University, Non-Interventional Ethics Committee (2015/645).

Informed Consent: All patients included were informed about the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Consept: F.A., B.D., Design: F.A., F.A., P.O., B.D., Data Collection or Processing: S.G.T., F.A., Analysis or interpretation: S.G.T., F.A., B.D., Literature research: S.G.T., B.D., Writing: F.A., P.O., B.D.

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Original Article / Özgün Araştırma

Social and Psychiatric Results of Migration Among Women in a Western City in Turkey

Türkiye'de Bir Batı İlinde Göçün Kadınlar Üzerindeki Sosyal ve Psikiyatrik Sonuçları

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Immigration, refugees, women's health, mental health

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Abstract

Objective: The aim of this study was to assess the mental health of women who have been subjected to forced migration and the reasons of migration, in a western city sample of Turkey.

Materials and Methods: This cross-sectional study was conducted between 1st September-31st October 2012 in city Aydın. Systematic sampling method was used in the selection of the sample from the records of neighbourhoods. The number of people to be included in the study was calculated as 270. Data were collected via face to face interview by using an information form including demographics and Brief symptom inventory (BSI). BSI was developed by Derogatis and it is a short form of the symptom check list. The distribution of the continuous data was controlled by the Kolmogorov-Smirnov test. Mann-Whitney U Test for continuous data, chi-square test for discontinuous data were used. Type-1 error was accepted as 0.05.

Results: Migrant women stated the basic reason for migration as "employment purposes". The median value of anxiety variable in the migrant group was 0.38 (0.15-0.63) while median value was 0.30 (0.08-0.38) in the non-migrants (p=0.016). The median value of somatization score in migrants was calculated as 0.66 (0.22-1.11) and this value was found as higher than the median value of the same in non-migrants, which was 0.33 (0.11-0.55) (p=0.003). There was no significant difference in other BSI subscales' scores between migrant and non-migrant groups, apart from anxiety and somatization. Considering the use of health services, migrant women use primary health care services more than non-migrants.

Conclusion: The results of this study show that; forced migration negatively impacts women's mental health; that the migrants are prone to anxiety and that the migration increases the somatization.

Öz

Amaç: Bu araştırmanın amacı; Türkiye'nin bir batı ili örneğinde, göçün nedenlerini ve zoraki göç eden kadınların akıl sağlığını değerlendirmektir.

Gereç ve Yöntemler: Araştırma, kesitsel türde olup, 1 Eylül-31 Ekim 2012 tarihleri arasında Aydın ilinde yapılmıştır. Örnek seçimi için mahalle kayıtlarından sistematik örnekleme yöntemi kullanılmıştır. Örneklem büyüklüğü, Aydın'da toplam 270 kişi olarak olarak hesaplanmıştır. Araştırma verileri, demografik bilgiler ve kısa semptom envanteri (KSE) içeren bir bilgi formu ile yüz yüze görüşülerek toplanmıştır. KSE,

Derogatis tarafından geliştirilmiş olup, belirti tarama listesinin kısaltılmış halidir. Sürekli verilerin dağılımı, Kolmogorov-Smirnov testi ile kontrol edilmiştir. Sürekli değişkenler için Mann-Whitney U Testi, nitel değişkenler için ki-kare testi kullanılmıştır. Tip-1 hata, 0,05 olarak kabul edilmiştir.

Bulgular: Göç etmiş olan kadınlar, göçün temel sebebi olarak "iş sebebiyle" olarak belirtmiştir. Göç etmiş olan kadınlarda anksiyete skoru ortanca değeri 0,38 (0,15-0,63), göç etmemiş olan kadınlarda ise 0,30 (0,08-0,38) olarak daha düşük bulunmuştur (p=0,016). Somatizasyon skoru, göç etmiş kadınlarda 0,66 (0,22-1,11) ve göç etmemiş kadınlarda 0,33 (0,11-0,55) olarak hesaplandı ve aradaki fark istatistiksel olarak anlamlı bulundu (p=0,003). Göç etmiş ve etmemiş kadınlar arasında KSE skorlarında anksiyete ve somatizasyon alt grubu haricinde anlamlı bir fark saptanmamıştır. Sağlık hizmeti kullanımında, göçebe kadınlar göç etmeyen kadınlara göre birinci basamak sağlık merkezlerini daha çok kullanmaktadır.

Sonuç: Bu araştırmanın sonucunda zoraki göçün, kadın akıl sağlığını olumsuz olarak etkilediği görüldü. Göçmenler, anksiyeteye daha yatkın olmakta ve göç somatizasyonu artırmaktadır.

Introduction

Immigration which can be seen as a social movement, is one of the fundamental ways for a change that affects every aspect of life from economy to health (1). People, especially as groups, move to another region by leaving their habitual residences due to a variety of reasons (2). In the past, the issue of immigration was addressed as internal and external migration. In the last twenty years, the concept of forced migration has started to be considered. Forced migration is a kind of immigration that arises when people move to another region involuntarily caused by natural or man-made disasters (3).

United Nations defines "internally displaced people" in a document named "guiding principles on internal displacement" as follows: "internally displaced people are people or groups of people who have been forced or obliged to flee or to leave their homes or places of habitual residence, in particular as a result of or in order to avoid the effects of armed conflict, situations of generalized violence, violations of human rights or natural or human-made disasters, and who have not crossed an internationally recognized state border" (4).

Forced migration has led to a variety of negative issues; in terms of demographic and environmental aspects and political, social and economic perspectives. On the other hand, in terms of health related outcomes, psychological problems created by the immigration process are at an incomparable rate as against other problems caused by migration (5). Forced migration, traumatic events, resettlement of unfamiliar environments increase the risk of psychiatric morbidity among immigrants (6). The prevalence of main psychiatric problems including posttraumatic stress disorders, depression or, anxiety disorders, vary among different migrant groups according to cultural differences, different instruments used or the opportunities given by the host population. In a systematic review prevalence rates for depression or anxiety were stated as approximately 20% in labour migrants whereas 44% among refugees (7). In the literature, there are studies on mental problems among people who have migrated to other countries from Turkey but there is no study on mental problems of people who have been exposed to forced migration within the country (8,9).

In Turkey, high rates of migration had been seen after 1980s from eastern and south eastern parts of Turkey to the western regions. In this period, the conflictual events that occurred in the eastern regions, caused people to be displaced involuntarily, falling within the forced migration group. These people were forced to create new residential areas in the metropolis. And they had to struggle with many problems in the new settlements.

In this study, selected research area had got greater number of immigrants from the eastern regions to Aydin.

The aim of the study is to determine the reasons of forced migration and its psychological consequences among women in Aydın, Turkey.

Materials and Methods

This cross-sectional study was conducted between 1st September-31st October 2012 in Aydın, a city in western Turkey with a population of 1.006.541 people during the research period (10). There are high immigration rates from Eastern regions to Aydın, because of economic reasons or conflictive events. Net migration rates were as following according to year periods; 2.8 ‰ 2012, 2.3 ‰ in 2013, 13% in 2014

(11). The total number of study population is 27 000, 85% of which were Kurdish origins. It was reported that the population migrated from eastern provinces to the research area after 1980. The prevalence of the migration among the women in the district was 84.9%. This information was learned from local government via personal communication.

Study Sample

Common mental disorders such as depression, anxiety and somatic complaints affect approximately one third of people in the community worldwide (12). Turkey Mental Health Profile study (1998) showed that the prevalence of mental health problems was 17.2% (13). There are some studies at regional level but there is no new generalized data in Turkey, currently. As mentioned above, assuming a prevalence rate of 20% (for depression/anxiety levels of labour migrants); the number of people to be included in the sample was calculated as 246 according to the following formula: $n=t^2pq/d^2$ (p=0.20; q=0.80; d=0.05). The sample size was calculated with the Epi Info-StatCalc program used in prevalence studies. Because beta type error was not considered in this program, it was not included in sample size calculation (14).

Assuming a missing of 10%, the goal was to reach 270 individuals in the population. According to the records, 4 000 people are the inhabitants of the district whereas 23 000 people migrated to the district. By the records of mukhtar (head of the neighbourhoods), a list of the women at the age of 18 and above was reached and then, the address information of the target population was taken via systematic sampling method. In total, 35 inhabitant women and 235 forced migrated women were selected according to the proportion in the population and they participated to the study. One questionnaire form of migrants had insufficient data, so that it was omitted in analysis.

Trained interviewers applied the questionnaire to the women by using the face-to-face interview technique in participants' houses.

Questionnaire

A questionnaire was applied to all women above 18 years living in houses where the sample was taken. Possible language problems were overcome by the help of their children who were able to speak Turkish. The questionnaire form consists three sections: socio-demographic, reasons for migration and frequency of health service usage and Brief symptom inventory (BSI). Reasons for migration classified according to a national study named "Survey on migration and displaced population, Turkey" (15).

BSI is a short form of the Symptom check list (SCL) formed as a result of works conducted by SCL-90-R (16). BSI was developed by Derogatis in order to perform a general psychopathological assessment both in a quick, reliable and valid way (17). BSI is a sample for individuals enabling them to identify themselves. It consists of 53 items that detect and measure various psychological symptoms. BSI was adapted into Turkish by Şahin and Durak in 1994 (18). Subscales of the scale is; anxiety, depression, negative personality, somatization and hostility.

The Sub-Scales Used Are Defined As Following

Anxiety; includes symptoms and behaviours like anxiousness, tension, worry, fear, nervousness, panicking, the feeling of nausea, diarrhoea, frequent urination, a feeling of asphyxiation, excessively breathing. Depression; Includes symptoms and behaviours like pessimism, moodiness, feeling of unhappiness, indecisiveness, loneliness, generally being indifferent to life and suicidality. Negative personality; Includes symptoms like finding oneself inadequate, feelings oneself ineffective, worthless and guilty by feeling lowly and inferiority complex. Somatization; includes some somatic complaints ongoing for years recurrently not associated with physical reasons. Symptoms such as chest pain, abdominal pain, dyspnoea, nausea, fainting, and numbness in the body are defined under the somatization scale. Hostility; includes symptoms like incidence of shivering, nervousness, temper, anger, insecurity, perpetrating violence against others, fighting, beating, intending to harm others and to cause damage to property.

Three index scores which are the general determinants of mental health can be obtained from BSI (severity of illness index, Total symptom index (TSI) and Illness symptom index (ISI). For the calculation of the scores, for each question, the person responds to the scale is asked to mark the one of the following options as an answer: "None" (0 points), "A little" (1 point), "Moderate" (2 points), "Quite" (3 points), "Too many" (4 points).

The total score obtained for each subscale is calculated by dividing it by the number of items in the subscale. Higher scores suggest higher levels of

psychological symptoms:

Severity of index (SOI) level showing the level of stress, are calculated by dividing the total of the subscales by 53; it ranges from 0 to 4.

TSI is the total score obtained as a result of the assumption of all positive values as 1 apart from the items marked as 0; it ranges from 0 to 53.

ISI, is obtained by dividing the sum of the subscales by TSI.

The study protocol has been designed in conformity with Declaration of Helsinki (Seoul, October 2008) and necessary permission was obtained from the Ethics Committee of Aydın Adnan Menderes University, with the protocol number 2012/114.

Statistical Analysis

The data was analysed with software of SPSS 17.0 version. Normality distribution of continuous data was analysed with histogram and the Kolmogorov-Smirnov test. Descriptive statistics were defined by using median values and 25 and 75 percentile values for not normally distributed variables and defined using the mean ± standard deviation for normally distributed variables. Chi-square test was used to compare categorical data and Mann-Whitney U test was used to compare continuous data. Type-1 error (α) level was assumed as "0.05".

Results

Total of 269 women (234 migrant women and 35 non-migrant women) were included and they accepted to fill the questionnaire. The mean age of the migrant group was 38.8±12.6 years, and the mean age of the non-migrant group was 31.9±11.2.

Reasons for migration were stated as, personal reasons (28.8%), familial reasons (28.2%) and spousal reasons (27.2%). Sub-group interrogations of the stated reasons have been reported as the "employment purposes" as the basic reason for migration.

11.3% of migrated women affected from migration socially declared themselves as having "homesickness".

Table 1. Characteristics of migrants and non-migrants

	Migrantsϕ		Non-migrantsϕ			
	n	%	n	%	χ^2	p
Education (n=269)*						
Primary education, or less	223	95.3	25	71.4		<0.001∀
Above primary education	11	4.7	10	28.6		
Total monthly income per house (₺) (n=267)*						
1000 Turkish liras and below	173	74.2	19	55.9	11.704	0.003
1001-1500 Turkish liras	51	21.9	9	26.5		
1501 Turkish liras and above	9	3.9	6	17.6		
Marital status (n=269)*						
Married	205	87.6	25	71.4	6.428	0.011
Single (widow or living seperate)	29	12.4	10	28.6		
Number of people living in the house (n=269)*						
4 People and below	72	30.8	20	57.1	9.411	0.002
5 People and above	162	69.2	15	42.9		
Primary health care service use (n=267)*						
Prefer	142	61.2	17	48.6	2.016	0.156
Do not prefer	90	38.8	18	51.4		

*Statistical tests were done according to the people answered the question, ϕColumn percentages are shown in table-1, ∀Fisher-Exact test was used

Table 2. The effects of forced migration on mental health symptoms of women

Median		Migrants		Non-migrants		U	p
		Median	25–75 p*	Median	25–75 p*		
Brief symptom inventory Scores	Anxiety	0.38	0.15-0.63	0.30	0.08-0.38	3063.50	0.016
	Depression	0.66	0.33-1.08	0.66	0.25-1.00	3799.00	0.565
	Negative personality	0.33	0.17-0.66	0.33	0.08-0.75	4074.00	0.993
	Somatization	0.66	0.22-1.11	0.33	0.11-0.55	2823.50	0.003
	Hostility	0.57	0.28-0.89	0.71	0.14-1.28	3827.00	0.530
	Severity of illness index	0.49	0.32-0.81	0.49	0.13-0.74	3699.50	0.357
	Total symptom index	18.00	12.00-25.00	17.00	7.00-25.00	3834.50	0.544
	Illness symptom index	1.45	1.21-2.00	1.32	1.00-1.83	3301.00	0.064

*25 and 75 percentiles

Although they migrated for employment purposes, 26.7% of migrant women indicated that migration affected them economically, 58.8% of them stated that they did not have good economic situation and 10.6% of migrated women stated that they wanted to leave the place where they lived currently.

In migrant group, only 4.7% of participants continued education after primary education, whereas this ratio was 28.6% in non-migrant group and the difference was statistically significant (p<0.001). 74.2% of migrants had income monthly lower than 1000 Turkish Liras, this ratio was 55.9% in non-migrants (p=0.003). Migrants lived in more crowded houses than non-migrants (p=0.002). 87.6% of migrants and 71.4% of non-migrants were married, and this difference was not significant (p=0.011) (Table 1).

Considering the use of health services, more than half of the migrant women (61.2%) were preferring primary health care services whereas this ratio was 48.6% in non-migrant women. Primary care services were more used by migrant populations but the difference was not significant (p=0.156).

It was found that forced migration had adverse effects on the mental health of women in terms of anxiety and somatization (p<0.005) (Table 2). Migrants were found more prone to anxiety than those who did not migrate. The median value of anxiety score in the migrants was 0.38 (0.15-0.63) and it was 0.30 (0.08-0.38) in the non-immigrants (p=0.016). Also median value of somatization score was also higher than the median value of the non-migrants such as 0.66 (0.22-1.11) to 0.33 (0.11-0.55) (p=0.003).

In migrants, median values of Severity of illness index, TSI and ISI were respectively 0.49 (0.32-0.81), 18.00 (12.00-15.00), 1.45 (1.21-2.00) and in non-migrants these values were respectively 0.49 (0.13-0.74), 17.00 (7.00-25.00), 1.32 (1.00-1.83) (p=0.357 (SOI), p=0.544 (TSI), p=0.064 (ISI). There was no significant difference in BSI subscales' scores between migrant and non-migrant groups.

Discussion

The ratio of those who completed primary education in the sampling group was very low in migrants. In Aydın province, according to the Turkey National Education Statistics database, the ratio of women older than 15 years and those graduated from primary education or not completed was 72% in 2012 and this rate was similar to the non-immigrant group (19). Migrants might not have the opportunity to go to school enough or they might have a lower educational level and cultural character in the place where they had migrated from. A study conducted by Borjas in 1995 supports the low level of education in migrants (20).

In the study group, 25% of migrants had a monthly income of more than 1000 TL per month (the minimum wage in 2012 was about 740 TL) (21). In a refugee study in 2009, conducted in Van province, 10% of those surveyed had a monthly income of more than 500 TL per month (minimum wage was

about 550 TL) (22). In contrast, in a survey on Russian migrant women in Antalya province in 2013, 84% of women had a monthly income of more than 1000 TL per month (the minimum wage was about 800 TL) (23). In a study, it was stated that economic problems could be transferred from generation to generation in migrants. Many factors, mainly migration reasons, might affect the monthly income of migrants. As mentioned at the beginning, economic problems are one of the reasons of migration and migrations could be prevented via improving economic status and job opportunities It is important to create income generating opportunities in the areas people live in. Nowadays, in Turkey, immigration from the city to the city has increased a lot and that causes urban poverty. Those who migrate live mostly in the suburbs and in bad conditions, so that, this affects their health status, negatively. Enough current data couldn't be found to compare, so that new studies about this subject are required.

In migrants, the marriage status ratio was higher (69.2% vs 42.9%), because the most important reasons for migrating were their familial and spousal reasons. However, it seemed that migrants were living more crowded in their houses. In literature, there was not enough evidence to explain this relation. However, there might be many reasons such as migration of migrants to near relatives, migration from a high birth rate region, cultural features.

The use of primary health care services was higher in migrants (61.2% vs 48.6%). There were some studies which showed that migrants had difficulty in using health services. For this reason, the preference ratio of primary health care services might be higher in terms of easy accessibility. For migrants, obligation to pay extra to expensive secondary or tertiary health care services might cause migrants to prefer free primary health services. However, further research is needed on why migrants prefer primary health care services.

The cause of migration is one of the most important factors affecting mental state. While in voluntary migrations mental problems are occurred less, those problems increase in forced migration (24). Our study findings also support that view.

In the study of Aker et al. (25) (2002), 80% of women stated that they have lost their social environment while staying away from the family and relatives; 65% of them (especially middle-aged women and above) complained that they could not adapt to the urban environment because of language barrier. Most of them did not have any communication with anyone other than people in their household. Almost all of the women (90%) stated that their psychological problems increased after migration to a new environment and especially middle aged women would like to return to their old settlements. In our study 10.6% of the migrant women stated that they wanted to leave their current settlement. Migration itself can be a stress source due to its characteristics. Stress is the factor that triggers the depression and thus migrant women are at risk of depression. It is a known fact that women are exposed to more biological and psychosocial stress factors than men as they lack employment opportunities and have low levels of education in Turkey (26). They can face with social problems such as gender inequality, poverty, role conflicts at home, low participation to decision making mechanisms (27).

In the study of Türkleş et al. (28) (2013), it is noted that migrant women living in a southern city of Turkey experienced problems in intrafamily communications, in showing appropriate emotional responses, paying the necessary attention and general functions of the family. In another study aiming to evaluate the behaviours of migrant and non-migrant women living in a western city of Turkey, it is determined that women who migrated was found to have lower health related scale scores while coping with the stress (29). All of those can lead to the occurrence of mental health problems in women.

Sir et al. (30) (1998) assessed the mental health of a group forced migrated individuals by using SCL-90-R and Beck Depression Inventory (BDI). The results of the migrant group were compared with the non-migrant group living in the same area. When comparing the scores of SCL-90-R, significant differences were detected in all subgroups except anger. According to these results it is interpreted that all of the psychological characteristics of the migrant group were affected. General symptom index (GSI), was found as higher in migrant women having low level of education (30).

In our study, the mental health of women was assessed by BSI. As a result of our study, it was found that anxiety and somatization were high in the

migrant group in comparison to non-migrant group. Immigration status leads to the increase in inclination for anxiety and affects somatization in accordance with to the results of other studies in the literature. The high incidence of somatization between migrants has been demonstrated in various studies (8,31)

This was suggested to be associated more with anxiety and depression. In the study of Sir et al. (30) (1998) somatization was found significantly higher in the group of migrants. In the study of Westermeyer et al. (8) (1989) it was suggested that somatization was related with education. While the somatic complaints are sometimes the symptoms of depression and those also can be a projection method be used to draw the other people's attention. As a result of the studies of Sir and Bayram (30) (1998) it is noted that forced migration had adverse effects on mental health and women migrants experienced more emotional distress than man.

Regardless of under which circumstances migration took place, men and women do not experience it in the same way. Women experience the effects of migration in a different way than men, due to gender inequality. Migration, itself is the cause of trauma, feeling of statelessness and alienation, and in case of a forced migration it is observed that women may become more introverted and isolated. They experience problems about daily life (shopping, using the health services, childcare related work, etc.) and have to live isolated without any integration in the social life (24,25). Language barrier is one of the biggest problems of most women especially for middle-aged women. Men might have chances to learn Turkish by leaving their habitual residences for employment or military service purposes, whereas women do not have such a chance since they live isolated in their houses (26).

As mentioned above, there are lots of difficulties (such as insufficient income, worries about health, education etc.) for migrants to cope with. Inequalities can also cause social and psychological problems. Migrants have less facilities and that could cause psychological problems, too (32).

The most important limitation of this study was that we just asked the symptoms of diseases to the participants instead of detailed psychiatric interview. Therefore, it didn't reflect a psychiatric diagnosis. Another difficulty was language problem. We dealt with this problem via the use of translators who were participants' children. Although transportation seems to be a problem for this study, we had no problem. Since, participants were living in the near neighbourhoods to our institution, mostly.

Conclusion

The factors including the problems of adaptation to a new culture, language barriers, lacking adequate social support, low socio-economic level, low employment opportunities and low standards of working conditions faced by migrants cause a variety of mental health problems. These problems are more frequently seen in women than men. Using a combination of various psychological practices together would be beneficial in order to determine in detail the health and mental health problems of victims of migration. For example, we apply BSI inventory in line with our own means in this study. In the new researches to be conducted using BSI alongside with the beck depression inventory, multidimensional anger scale or social comparison scale will allow the identification of the problems in detail.

The problem of internal displacement and forced migration should be considered as public health issue at the national level. The social integration projects for victims of migration need to be put into practice. There should be projects for solutions to be designed and implemented firstly regarding the problems of language, education and culture, then regarding maternal and child health problems, psychological counselling and rehabilitation centres. In health care institutions, public health and mental rehabilitation services should be expanded and the access to these services should be facilitated. In order to provide such services, the language barrier should be overcome and there should be solutions for the language problem. The health care staff that will provide the care should be trained about the specific problems of victims of migration. In addition, a variety of job opportunities should be created to strengthen migrants' socio-economic levels.

It should be noted that the victims of migration that are supported socially and psychologically can deal more effectively with existing problems, and they can adapt more quickly and easily into psychosocial society in which they live.

Ethics

Ethics Committee Approval: Aydin Adnan Menderes University, School of Medicine Non-Interventional Clinical Research Ethics Committee (Protocol Number: 2012/114)

Informed Consent: It was not taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: F.A., O.O., E.D.E.K., Design: F.A., O.O., P.O., E.B., Data Collection or Processing: O.O., F.Y., Analysis or Interpretation: F.A., F.Y., P.O., E.D.E.K., Literature Search: O.O., F.Y., Writing: F.A., O.O., F.Y.

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Original Article / Özgün Araştırma

The Effects of Paracetamol and Ibuprofen on Smooth Muscle Response of the Bronchospasm: An *In Vitro* Study

Parasetamol ve Ibuprofenin Bronkospazm Oluşturulmuş Bronş Düz Kas Dokusunda Etkileri: In Vitro Çalışma

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Keywords
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Abstract

Objective: Bronchospasm is a very important complication that can be encountered during the post-operative and intraoperative periods. This complication may be caused by surgery, anesthesia, or patient-related issues. Many analgesics are preferred during the intraoperative period for post-operative analgesia. In this study, we aimed to investigate the effects of ibuprofen and paracetamol on rat bronchus with supramaximal tonus as a model of bronchospasm under *in vitro* conditions.

Materials and Methods: Totally, 20 male rats were used in our study. After the ketamine anesthesia, the left main bronchus of each rat was removed and suspended in the organ bath in Krebs solution. Four rat bronchi were excluded because of not demonstrating viability with atropine and acetylcholine. After demonstrating the viability of the rats' bronchi (n=16), acetylcholine was applied to produce supramaximal contraction. The rats' bronchi with supramaximal contraction were randomly divided into two groups. Paracetamol was applied to group 1, and ibuprofen to group 2. The contraction responses of each group were recorded and compared statistically.

Results: While a statistical significance was not detected regarding the supramaximal contraction in group 1 with a mean of 0.18±0.07% ($p>0.05$), tonus was reduced to 6.79±0.28% ($p<0.05$) in group 2, and the relaxation response reached the baseline tonus in this group.

Conclusion: Intraoperative analgesia is very important in preventing post-operative complications and ensuring patient comfort. In general, opioids and concomitant nonsteroidal anti-inflammatory or paracetamol group drugs are preferred intraoperatively for post-operative analgesia. In our study, although there was no effect of paracetamol on rat bronchi with supramaximal tonus, ibuprofen showed an unexpected significant relaxation response. In conclusion, ibuprofen may be preferred much more the than paracetamol in patients with high risk of clinical bronchospasm.

Öz

Amaç: Bronkospazm post-operastif ve intraoperatif dönem boyunca karşılaşılabilen çok önemli bir komplikasyondur. Bu komplikasyon cerrahi, anestezi ve hastaya ait nedenlerle oluşabilmektedir. Post-operatif analjezi oluşturmak için intraoperatif dönemde rutinde pek çok analjezik tercih edilmektedir. Bizde bu çalışmada

in vitro şartlarda bir bronkospazm modeli olarak supramaksimal tonuslü rat trakeasında intravenöz analjeziklerden ibuprofen ve parasetamolün etkilerini görmeyi amaçladık.
Gereç ve Yöntemler: Çalışmamızda toplam 20 erkek rat kullanıldı. Ketamin anestezisi sonrası her ratın sol ana bronşları çıkarılarak Krebs solüsyonunda organ banyosuna asıldı. Dört rat bronşu asetilkolin ve atropine cevap alınamadığı için çalışma dışı bırakıldı. Canlılığı kanıtlanan rat bronşlarına (n=16) asetilkolin uygulanarak supramaksimal kontraksiyon oluşturuldu. Supramaksimal kontraksiyon oluşturulan rat bronşları randomize olarak iki gruba ayrıldı. grup 1'e (n=8) parasetamol, grup 2'e (n=8) ibuprofen uygulandı. Her bir grubun kontraksiyon cevapları kaydedildi ve sonra istatistiksel olarak karşılaştırıldı.
Bulgular: Supramaksimal kontraksiyonda grup 1'de ortalama %0,18±0,07 ile istatistiksel olarak anlamlı bir değişiklik saptanmazken (p>0,05) grup 2'de ortalama %6,79±0,28 (p<0,05) tonusu düşüşü izlenerek bazal değerlere indiği belirlendi.
Sonuç: İntraoperatif analjezi post-operatif komplikasyonların önlenmesinde ve hasta konforunun sağlanmasında çok önemlidir. Genel olarak post-operatif analjezi için intraoperatif olarak opioidler ve beraberinde non-steroid anti-enflamatuvar ilaçlar veya parasetamol grubu ilaçlar tercih edilmektedir. Çalışmamızda tonusu artırılmış bronş dokusunda "*in vitro* bronkospazm modeli" parasetamolun herhangi etkisi olmazken, iboprofenin beklenilenin aksine istatistiksel olarak anlamlı oranda gevşeme cevabı verdiğini saptadık. Sonuç olarak eğer *in vivo* çalışmalarla da desteklenirse klinik olarak bronkospazm riski yüksek olan hastalarda ibuprofenin parasetamolden daha öncelikli olarak tercih edilebileceğini düşünmekteyiz.

Introduction

Airway spasms are common and increase surgical risk (1-3). Bronchospasm is an undesirable phenomenon in all phases of operation and anesthesia. There are also studies supporting that endotracheal intubation and general anesthetic agents increase the incidence of bronchospasm and post-operative bronchospasm by 20% for both regional and general anesthesia (4,5). Many studies have also been conducted on pediatric surgical patients, in whom one of the major concerns of anesthesiologists is the identification of perioperative respiratory adverse events and associated risk factors (6). Especially in interventions as removal of respiratory foreign body and procedures associated with the upper respiratory tract, this risk is increasing (7,8). Intravenous analgesics are often preferred in post-operative pain prophylaxis. However, in the literature, the bronchospasm risk of these intravenous analgesics is small. In this study, we tried to show concrete effects of ibuprofen and paracetamol, and we applied the model of bronchospasm to the bronchial smooth muscle of rat bronchus which was simulated under *in vitro* conditions.

Materials and Methods

Twenty male rats (four to six-month-old, about 350-400 g) were obtained from Experimental Animal Center of Aydın Adnan Menderes University (ADU), and all experiments were performed in accordance with the principles and guidelines of ADU Animal Ethical Committee's approval (HADYEK 64583101/2016/56).

Experimental Model

Krebs-Henseleit solution contains (g/L): glucose 2, $MgSO_4$ 0.41, KPO_4 0.16, KCl 0.35, NaCl 6.9, CaCl 0.373, $NaHC0_3$ 2.1 (pH=7.4) in isolated tissue bath. The buffer solution was oxygenated with 95% O_2 and 5% CO_2. During the equilibrium period in the organ bath, the Krebs solution of the organ bath was washed for four times in one hour (once a 15-minute-period), 1 g basal tension was slowly supplied. All rats were anesthetized with 50 mg/kg ketamine. After the anesthesia, while heartbeat was continuing, trachea and left main bronchus were removed with thoracotomy and sternotomy as rings sized 3 mm and suspended with 1 g rest tension in 10 mL organ bath.

After the left main bronchi of rats were removed, all rats were decapitated and sacrificed. Isometric contractions of circular smooth muscles were measured with the MAY frequency-doubling technology 10-A® transducer. After the viability of the tissues was demonstrated with acetylcholine (Ach) and atropine, washed tissues were kept waiting until they reached the basal tonus. Four rat bronchi were excluded from the study because of not demonstrating viability with atropine and Ach. The bronchi that completed these steps were considered as alive. After demonstrating the viability of the rat bronchi (n=16), Ach was applied to produce supramaximal contraction. Sixteen rats, which produced at least 7% increase in Ach supramaximal contraction and provided a plateau for at least 15 minutes were included in the study. Two groups were assigned to a random number table. Paracetamol ($1x10^{-1}$ M) was administered to group 1

in the supramaximal contraction and ibuprofen ($1x10^{-1}$M) in group 2 in the supramaximal contraction. The results were recorded in the Acknowledge MP 100® program.

Statistical Analysis

The normality test of tonus, before and after administering to the groups of ibuprofen and paracetamol, was performed by Kolmogorov-Smirnov test and data were log transformed for normal distribution. After logarithmic transformation data were normally distributed. All data were shown as mean, standard deviation, and 95% confidence interval (CI). Comparisons of pre- and post-measurements in each drug were made using the paired sample t-test for normally distributed data in groups. The comparisons of relaxion rate of two drugs were done by using independent samples t-test. SPSS 22.0 program were used and $p<0.05$ was considered statistically significant.

Results

In the 10 mmoL group of ibuprofen, it was determined that the level of supramaximal tonus was at 0.41±0.93 before implementation, which decreased to the level of 0.34±0.90 after implementation. The reduction in tonus was statistically significant (estimated mean difference, -0.41; 95% CI, 0.038 to 0.092; p=0.001 (Figure 1). Mean tonus decrease rate for ibuprofen was 1.423±0.2% (Figure 2).

However, in the 20 mmoL group of paracetamol, level of supramaximal tonus was at 0.20±0.85 before implementation, which had no change in the level of 0.20±0.85 after implementation. The difference was not statistically significant [estimated mean difference, 0.20; 95% CI, -0.006 to 0.002; p=0.340] (Figure 1). Mean tonus change rate for paracetamol was 0.213±0.6% (Figure 2).

In the paracetamol group, the duration of reaching supramaximal contraction after Ach was 190±5 seconds, while 180±4 seconds in the ibuprofen group but there was no statistical significance (p>0.05) (Figure 3). In group 1, supramaximal tonus after paracetamol could be kept for 500 s (Figure 3).

After ibuprofen administration, it showed a relaxation, down to much below from baseline tonus before Ach, within a mean of 270±8 s and this tonus was preserved for 500 s (Figure 3).

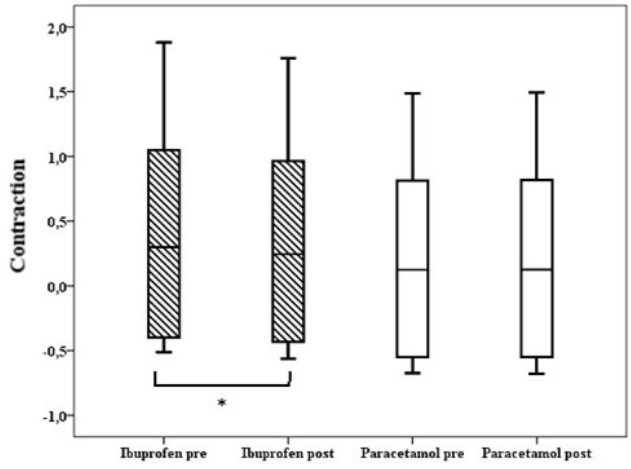

Figure 1. Box plot representing the initial (pre) and last (post-) % contractions of bronchioles after Ibuprofen and Paracetamol. Ends of the whiskers represent the 10th and the 90th percentiles. Horizontal lines represent mean values. Paired sample t-test results *p<0.001

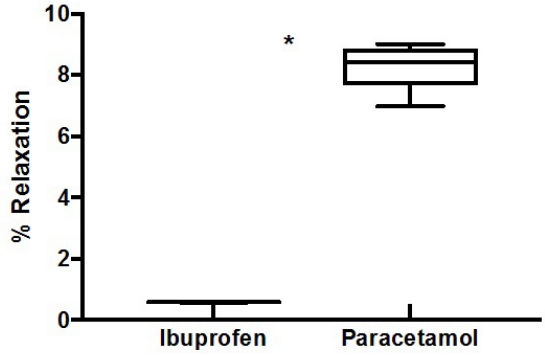

Figure 2. The relaxation rate of groups after supramaximal contraction *p<0.001

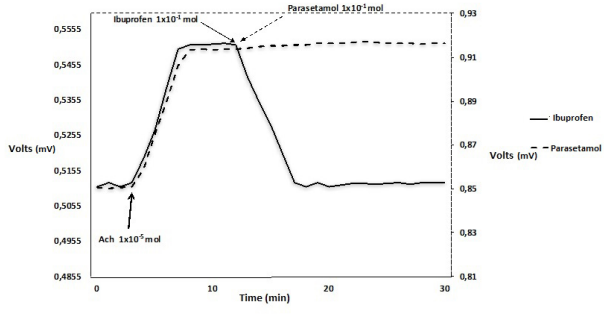

Figure 3. The effects of ibuprofen and paracetamol on alteration of ach-induced contractile response. Straight line denotes the contraction changes on ibuprofen. The dotted line denotes the contraction changes on Paracetamol

Discussion

In our experimental study, we found that ibuprofen gave a response as a muscle relaxation in contrast to the expected increase in supramaximal bronchial muscle tissue tonus. Paracetamol did not cause any change in muscle tone.

In this study, we measured the smooth muscle response of the bronchial tissue to ibuprofen and paracetamol, which we use most frequently for analgesic purposes, under *in vitro* conditions, in the organ bath. We evaluated the responses obtained with ibuprofen and paracetamol, which we added in supramaximal contractions after increasing tonus of bronchial tissue to simulate bronchospasm. We found no muscle response to paracetamol in the smooth muscle of the bronchus, while ibuprofen caused a significant muscle relaxant response in the smooth muscle of the bronchus in the supramaximally contracted state.

Airway spasm is very common and one of the most important and life-threatening complications. Regarding the etiology of this spasm, there is a wide range of causes, from an upper respiratory tract infection to an underlying allergic reaction to anesthetic medications. Except for the predictable ones, the sudden and unpredictable development of airway spasm, which is a serious problem for both the surgeon and the anesthetist, is not less at all (9).

Non-steroidal anti-inflammatory drugs show their analgesic and anti-inflammatory effects by inhibiting COX-1 and COX-2. Inhibition of these enzymes inhibits the release of pathogenic inflammatory and physiological mediators (10). There are many clinical studies showing that ibuprofen increases the frequency and morbidity of bronchospasm, resulting in exacerbations in asthmatic patients (11-13). Some investigators have reported severe and fatal asthma attacks due to ibuprofen (14,15).

In recent years, the risk of acute bronchospasm induced by ibuprofen in children with asthma has been questioned. There is little evidence related to the increased morbidity in pediatric asthmatic patients. In addition, the inflammatory pathogenesis of asthma can reduce morbidity in asthmatic children due to the anti-inflammatory effect of ibuprofen. This feature of ibuprofen causes an interesting possibility of therapeutic benefit, at least for some children with asthma (16). In an *in vivo* study, non-steroidal pharmaceuticals have been shown to result in reduced guinea-pig tracheal tone by inhibition of intramural biosynthesis of prostaglandins (17). In another study, following oral administration of ibuprofen resulted in a 45% to 80% improvement in forced expiratory volume 1 in spirometric measures (18). Because airway responses occur through many different mechanisms, the airway responses of ibuprofen obtained in clinical trials show differences. In our experimental study, we objectively have shown that bronchial smooth muscle tissue shows distinctive muscular relaxation with ibuprofen in the bronchial tissue bath.

Paracetamol appears to be the most reliable analgesic preparation in analgesic-dependent bronchospasm risk (esp. in asthmatic cases) (19). In our study, it caused no effect on the supramaximal tonus of the bronchial smooth muscle cells. In a study by Corominas et al. (20) a paracetamol-induced asthma attack was mentioned. In some meta-analyses, associations seem to be present between paracetamol use and asthma development, and paracetamol has been reported to increase asthma risk by a factor of 6 (21,22). A long-lasting relationship between asthma/chronic airway spasm and paracetamol has been shown in publications, but it is evident that its acute use is reliable in patients who are not at risk. In our experimental study, we applied that paracetamol on the bronchial tissue in supramaximal tonus and did not get any muscular response.

Ibuprofen and paracetamol have both oral and intravenous (IV) preparations. Oral or IV use does not alter their bioavailability (23). However, there are a limited number of available analgesic agents via IV route. There are many clinical studies showing the difference of effects of ibuprofen, paracetamol, and IV analgesics on airway spasms (24). There is no organ bath study that demonstrates the effects of the drugs on specific bronchial muscle tissue. We compared the effects of two drugs on the bronchial smooth muscle at supramaximal contraction. Both analgesics did not cause an increase in muscle tone of the bronchial smooth muscle. Ibuprofen was shown to give a significant relaxation response when compared to paracetamol. In the light of these data, ibuprofen is more effective than paracetamol for the relaxation of the contracted bronchial smooth muscle.

Conclusion

Although with this study, we were able to accomplish objective measurements of the effects of a single dose of the drugs on tonus-enhanced bronchial tissue, it needs to be supported by clinical studies measuring and comparing the effects of different doses on various airway tissues with different tonus.

Ethics

Ethics Committee Approval: ADU Animal Ethical Committee's approval (HADYEK 64583101/2016/56)

Informed Consent: It was not taken.

Peer-rewiev: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O.E., V.K.E., Concept: A.O.E., V.K.E., Design: A.O.E., S.Ö., Data Collection or Processing: A.O.E., V.K.E., M.Y., nalysis or Interpretation: A.O.E., V.K.E, S.Ö., M.Y., Literature Search: A.O.E., V.K.E., Writing: A.O.E., V.K.E.

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

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Original Article / Özgün Araştırma

Arthroscopic Decompression in Subacromial Impingement Syndrome: An Overview of Our Outcomes

Subakromiyal Sıkışma Sendromunda Artroskopik Dekompresyon Sonuçlarımız

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Abstract

Objective: Subacromial Impingement syndrome (SIS) is a common cause of shoulder pain due to compression of rotator cuff muscles. We aimed to compare preoperative and postoperative functional and radiological features after arthroscopic decompression in patients with SIS.

Materials and Methods: Forty patients (22 male/18 female) with mean age of 49 (21-76) undergone arthroscopic decompression for SIS. The mean follow-up length was 12 months. Before and after the surgery functional and radiological evaluations were performed. Constant shoulder scoring technique was used for evaluating the shoulder functions. The subacromial distance was measured on the sagittal magnetic resonance imaging sections. In addition, preoperative and postoperative Constant shoulder scores of 15 (37.5%) patients with a history of preoperative trauma and 14 (35%) patients with chronic disease were compared separately with the other patients.

Results: Neer and Hawkins tests were positive in 39 (97.5%) patients preoperatively and only 2 (5%) patients had positive results postoperatively. The median score of the preoperative subacromial distance was 9.3 (8.6-9.8) while the median score was 10.9 (9.9-11.8) in the postoperative measurements. The preoperative median value of the Constant shoulder score in all the patients was 11.5 (5-21) and the postoperative median value was 80 (61.25-85.5). While 36 (90%) patients had night-time pain preoperatively, no patients had postoperatively. These values were significantly decreased after surgery ($p<0.001$). Preoperative postoperative Constant shoulder scores of 15 (37.5%) patients going through preoperative trauma and 14 (35%) patients with chronic disease were not significantly different compared to the other patients.

Conclusion: Arthroscopic decompression is effective and safe in the treatment of stage 2 and 3 SIS. The subacromial distance should be recognized as an important criterion while managing SIS. Previous history of a chronic disease or trauma does not affect the outcome of the treatment in the patients suffering from SIS.

Keywords
Arthroscopic decompression, subacromial impingement, Surgery

Anahtar Kelimeler
Artroskopik dekompresyon, Subakromial sıkışma, Cerrahi

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Öz

Amaç: Rotator cuff kaslarının sıkışmasına bağlı oluşan Subakromial Sıkışma sendromu (SSS) omuz ağrısının sık sebeplerindendir. Biz fonksiyonel ve radyolojik açıdan SSS nedeniyle artroskopik dekompresyon cerrahisi öncesi ve sonrası bulguları karşılaştırılmasını amaçladık.

Gereç ve Yöntemler: SSS nedeniyle artroskopik dekompresyon yapılan ortalama yaşı 49 (21-76) olan 40 (22 Erkek/18 Kadın) hasta çalışmaya dahil edildi. Ortalama takip süresi 12 ay idi. Ameliyat öncesi ve sonrası fonksiyonel ve radyolojik açıdan değerlendirme yapıldı. Omuz fonksiyonlarını değerlendirmede Constant omuz skorlaması kullanıldı. Omuz sagittal manyetik rezonans görüntüleme kesitlerinden her iki omuzda subakromiyal mesafe ölçüldü. Ayrıca preoperatif travma öyküsü olan 15 (%37,5) ve kronik hastalığı olan 14 (%35) hastanın preoperatif ve postoperatif costant omuz skorları diğer hastalarla ayrı ayrı karşılaştırıldı.
Bulgular: Preoperatif 39 (%97,5) hastada Neer ve Hawkins testi pozitifken, ameliyat sonrası 2 (%5) hastada pozitif olarak saptandı. Preoperatif subakromiyal mesafe medyan değeri 9,3 (8,6-9,8), postoperatif ölçümlerde ise medyan değer 10,9 (9,9-11,8) idi. Constant omuz skoru tüm hastalarda preoperatif medyan değeri 11,5 (5-21), postoperatif medyan değeri 80 (61,2-85,5) olarak ölçüldü. Preoperatif 36 (%90) hastada gece ağrıları var iken postoperatif hiçbir hastada gece ağrısı görülmedi. Preoperatif ve postoperatif tüm bu değerler birbirleriyle karşılaştırıldığında istatistiksel olarak anlamlı olduğu görüldü ($p<0,001$). Preoperatif travmaya maruz kalan 15 (%37,5), kronik hastalığı olan 14 (%35) hastanın preoperatif postoperatif costant omuz skorları diğer hastalarla karşılaştırıldığında anlamlı bir fark görülmedi.
Sonuç: Evre 2-3 SSS'nin tedavisinde artroskopik dekompresyon etkin ve güvenilirdir. SSS yönetiminde subakromiyal mesafe ölçümü önemli bir kriter olarak kabul edilmelidir. SSS'li hastada kronik hastalığın olması ve ameliyat öncesi travmaya maruz kalmış olması tedavi sonucunu etkilememektedir.

Introduction

One of the frequent causes of shoulder pain is the Subacromial Impingement syndrome (SIS), resulting from the compression of the rotator cuff with the acromion, the coracoacromial ligament, the coracoid process, and the acromioclavicular joint during the glenohumeral joint movements, especially during flexion and rotation (1). SIS is associated with various degenerative changes occurring in the coracoacromial ligament, the anterior part of the inferior surface of the acromion, and sometimes in the acromioclavicular joint. While vascular, degenerative, traumatic, and mechanical factors are involved in the aetiology of SIS, it is caused mostly by repeated traumas, poor perfusion, or degenerative changes due to strenuous movements exerted with occupational or sports purposes (2). The vascular factors are encountered more commonly with the increasing age; however, mechanical factors are seen in association with the acromial types and spur formation beneath the acromion. None of these etiologic factors can explain the underlying pathologic mechanisms exclusively but it is suggested that various interactive combinations of these four factors, the vascular, degenerative, traumatic, and mechanic ones, lead to the development of SIS.

The diagnosis of SIS can be made by the clinical findings and by the radiograms and magnetic resonance imaging (MRI). The most frequently observed clinical finding in SIS is pain often localized in the anterior shoulder. The pain exacerbates during the night and sometimes it is felt in the neck. The elevation of the arm is very painful especially in the range from 60 to 120 degrees. This finding is called as *"Painful Arc"*. The pain is exacerbated by various activities including swimming, lifting the arm over the head, lifting heavy objects, driving, and throwing objects. The impingement test, lidocaine injection anterolateral to the acromion, is very important in the differential diagnosis. Neer and Hawkins test results are usually positive in these patients. Radiology is a key tool in the diagnosis of SIS. Regardless of the stage of the SIS, the following parameters are evaluated including the subacromial distance, the coracohumeral distance, the size of the hypertrophy in the acromioclavicular joint, the acromial type, and the discrepancies in the height of the centre of the humerus and that of the centre of the glenoid. A diagnosis of SIS will be likely if the subacromial length and the length of the shaft of the humerus are shorter than 7 mm and 12 mm respectively and if acromial types 2 or 3 are detected (3). Currently, the most sensitive, specific, and valid method in making the diagnosis of shoulder lesions is MRI. The pathological findings leading to the development of SIS can be detected with MRI including the supraspinatus tendinitis, a partial tear in the supraspinatus muscle, full thickness tears of the rotator cuff, and the hypertrophy of the acromioclavicular joint (Figure 1,2).

Neer described three pathological stages of SIS, which are treated either by conservative methods or by surgical interventions. The treatment is conservative in stage 1, which is characterized by oedema and haemorrhage. Stage 2 is characterized by fibrosis and tendinitis is treated with conservative methods primarily. A surgical intervention is indicated for the

patients with stage 2 SIS if they are unresponsive to the conservative treatment given up to 18 months. Stage 3 is characterised with the changes in the bones and ruptures of the tendons and treated by surgery (4). Arthroscopic decompression has recently been the most preferred method for the treatment of SIS as it is relatively less invasive and less costly, allowing for a faster recovery with a less likelihood for developing complications.

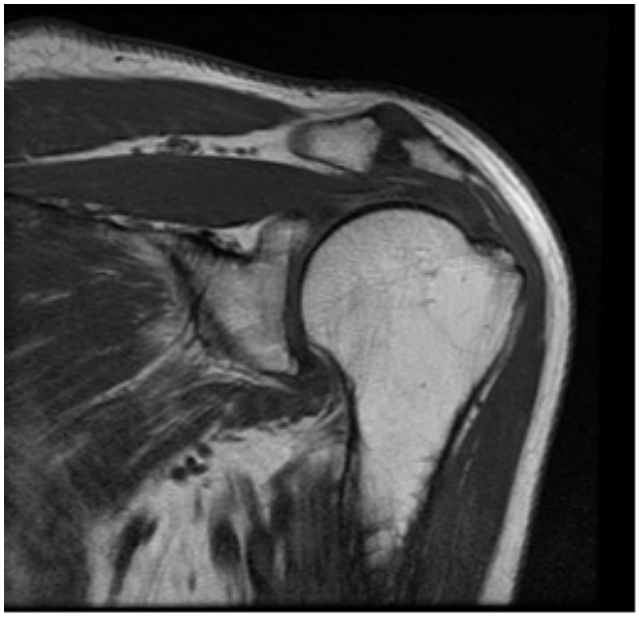

Figure 1. Acromioclavicular joint hypertrophy

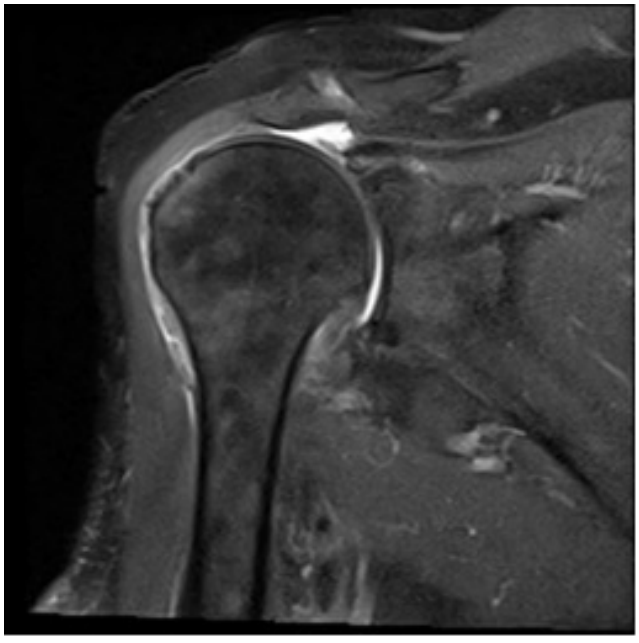

Figure 2. A full-thickness tear of the supraspinatus muscl

Materials and Methods

This study was aprroved by the Atatürk University Institutional Review Board (decision date and no: 12.06.2009-5/195). All volunteer patients included in this study were verbally informed about the study protocol and they signed the informed consent form.

Presenting to Atatürk University Faculty of Medicine, Department of Orthopedics and Traumatology between 2006 and 2010, a total of 40 patients with stage 2 and 3 SIS not responding to conservative treatment were included in the study. Of these patients, 22 (55%) were women and 18 (45%) were men with a mean age of 49 (21-76). In all patients, a thorough examination of the shoulder and Neer and Hawkins test along with the radiograms and MRI were performed in the preoperative period. Constant shoulder scoring technique was used for evaluation of the shoulder functions. The subacromial distance was measured in both shoulders in the sagittal sections of MRI. The study patients were categorized into trauma and chronic diseases subgroups according to their medical histories to be further evaluated. Arthroscopic decompression was applied to all patients in beach-chair position by the same surgical staff. General anaesthesia was applied in 4 (10%) patients while 36 (90%) patients were applied an interscalene block. A velpau bandage was applied to the patients with a hospital stay over 2.5 days. The exercises for physical rehabilitation started on the postoperative 4th day. Postoperative Constant shoulder scores and subacromial distances of the patients with a mean follow-up of 12 months were measured and compared with the preoperative measurements. Following the reapplication of Hawkins and Neer tests during the last follow-ups, patients having night-time pain were detected and compared with preoperative values. Postoperative preoperative Constant scores of patients exposed to trauma and having any chronic disease were compared with the scores of other patients.

Statistical Analysis

The conformity of continuous variables to normal distribution was examined by using Shapiro-Wilk test. Descriptive statistics were shown as median (25-75%) because none of the variables showed normal distribution. The Mann-Whitney U test was used to compare the preoperative-postoperative Constant

shoulder scores of the patients who were exposed to trauma and those with chronic disease with the other groups. Wilcoxon T test was used to compare preoperative postoperative Constant shoulder scores and subacromial distances. Descriptive statistics of categorical variables were shown as numbers (%). Preoperative postoperative Hawkins, Neer test and Mc. Nemar test was used to compare night-time pain.

Results

The median preoperative Constant shoulder score was measured as 11.5 (5.0-21.0); and the median postoperative as 80.0 (61.5-85.0) (p<0.001). The median score of the preoperative subacromial distance measurement was 9.3 (8.6-9.8) and the postoperative median score was 10.9 (9.9-11.8) (p<0.001) (Table 1).

Thirty-six (90%) preoperative patients had night-time pain; however, no night-time pain was observed in any postoperative patient. Neer and Hawkins test scores were found to be positive in 39 (97.5%) preoperative patients; however, they were observed to be positive in only 2 (5%) postoperative patients. A statistically significant difference was observed when comparing these scores with each other (p<0.001). Thirty-six (90%) preoperative patients had night-time pain; however, no night-time pain was observed in any postoperative patient. When all the preoperative and postoperative Constant scores were compared, it was found to be statistically significant (p<0.001).

The median preoperative Constant score was 8 (4-18) in the patients going through a trauma and 12 (5.5-27.5) in patients not going through a trauma (p=0.361). The median postoperative Constant score was 74 (58-86) in the patients going through a trauma and 81 (61.5-86) in patients not going through a trauma (p=0.600) (Table 2).

The median preoperative Constant score was 7.5 (3.7-18.7) in the patients with chronic disease and 12 (5.7-27.7) (p=0.380) in the patients not having any chronic disease. The median postoperative Constant score was 73 (57.2-86.2) in the patients with chronic disease and 81 (61.7-84) (p=0.552) in the patients not having any chronic disease (Table 3).

After treatment, 8 (20%) patients had biceps tendinitis, 2 (5%) had triceps tendinitis, and 4 (10%) had transient neuropraxia. Steroid injection was applied to the patients with biceps tendinitis at the 3rd month follow-up. No complication was observed in the patients undergoing 8 weeks of follow-up.

Table 1. Comparison of preoperative postoperative Constant score

	Preoperative median score	Postoperative median score	p
Constant	11.5 (5-21)	80 (61.25-85.5)	<0.001
Subacromial distance	9.3 (8.6-9.8)	10.9 (9.9-11.8)	<0.001

Table 2. The relation between trauma and preoperative postoperative Constant scores

	The patients going through a trauma	The patients not going through a trauma	p
Preop Constant	8 (4-18)	12 (5.5-27.5)	0.361
Postop Constant	74 (58-86)	81 (61.5-86)	0.600

Table 3. The relation between chronic diseases and preoperative postoperative Constant scores

	The patients with chronic disease	The patients not having any chronic disease	p
Preop Constant	7.5 (3.7-18.75)	12 (5.7-27.7)	0.380
Postop Constant	73 (57.2-86.2)	81 (61.7-84)	0.552

Discussion

It was described by Codman for the first time that the emergent changes in the supraspinatus tendon caused subacromial bursitis (5,6). In his study in 1972, Neer popularized the term “impingement”, suggesting that 95% of the rotator cuff tears were associated with the impingement phenomenon (7). Several studies conducted later also supported this hypothesis (8-10).

Several factors are involved in the aetiology of SIS, including the vascular, degenerative, traumatic, and mechanical ones. The vascular factors cause SIS increasingly more with the increasing age. The mechanical factors are associated with the acromial types and spur formation beneath the acromion. SIS was associated mostly with trauma in the patients younger than 55 years of age in our study. In our study patients older than 55 years, the hypertrophy of the acromioclavicular joint and the thickenings due

to spur formation in the inferior acromion were most common. In their study, Karabulut M. (11) reported that the major triggering causes of SIS were trauma and repetitive movements in 37.5% and 22.5% of the patients respectively, however, no triggering events were identified in 40% of the patients. Trauma was the triggering factor in 15 (37.5%) patients in our study. The parameters of the patients in whom trauma was the triggering factor were not statistically different compared to those in the other patient subgroups. The association of the chronic diseases with SIS is controversial. Morisson suggested that the response rates obtained in the patients with chronic diseases were relatively low, however, Conroy observed no differences in the patients in terms of the treatment response (12). Our study found that 14 (30%) patients suffered from chronic diseases, the most common ones being hypertension and diabetes respectively. The data collected from these patients were not statistically different from the other patients in the study.

Neer and Post report that in SIS, otherwise known as "*Painful Arc* syndrome", the pain is aggravated by movements (especially abduction and internal rotation) and especially during the night (13). The patients included in our study had complaints of a neck pain, a restricted range of motions in the shoulder, and pain during the night. These complaints were dramatically improved after the intervention. SIS was diagnosed in two patients treated with physical therapy due to a diagnosis of a cervical hernia and the pain was relieved also in these patients after the operation. We concluded that persistent neck pain should be thoroughly investigated in the physical therapy patient to exclude a potential diagnosis of SIS.

The primary treatment is conservative in the patients with stage 1 and 2 SIS. Ellman H. (14) reported successful results with relative resting, anti-inflammatory medications, physical therapy, rotator cuff strengthening exercises in stage 2 SIS.

Surgery is indicated in stage 3 patients and stage 2 patients who do not respond to the conservative treatment applied over a period of 18 months (4). Subacromial decompression has been recognised as a successful mode of surgical treatment in chronic SIS patients. Arthroscopic subacromial decompression has become a common method used in shoulder surgeries as arthroscopy is less invasive and has a less likelihood of leading to complications (15). Arthroscopic methods have started to be used by the end of the 1980s in subacromial decompression (16,17). Currently, arthroscopic acromioplasty is increasingly being used for the surgical treatment of the impingement syndrome. It is reported that the superiorities of arthroscopic acromioplasty over open surgeries become evident especially in the early postoperative period. In the literature, several studies report that arthroscopic surgery methods are superior to open surgery in the short-term as demonstrated by the alleviation of pain after the surgery, shorter length of hospital stay, and a shorter period of time required to go back to work. However, no differences were observed in the intensity of pain, the range of motion, and the muscle strength in the long-term (18).

Spangehl et al. (19) evaluated both techniques in their study and reported that the University of California at Los Angeles and patient satisfaction scores were similar after both open surgery techniques and arthroscopic surgeries. However, they reported that the results were more successful after the open surgeries in terms of the functionality and the reduction in the pain intensity. A proportion of reviews in the literature reported that similar results were obtained by both of these techniques, including the subjective and objective outcomes in the short and long term (19). In the view of these contradictory results in the literature, we have concluded that arthroscopic surgery is advantageous in evaluating intra-articular pathologies and the method is associated with a smaller scar size, however, it does not provide superior results in the long term compared to open surgeries.

Neer and Hawkins tests are highly important in making a diagnosis of SIS. In his study, Çalış et al. (20) showed that the most sensitive test was Hawkins with a sensitivity of 92.1%, followed by Neer with a sensitivity of 88.7% in making the diagnosis of SIS. In our study, Neer and Hawkins tests showed specificity rates of 98% consistent with being the most sensitive tests in making the diagnosis of SIS as reported in the literature.

The mean Constant score was 15 preoperatively, however, they were improved and found to be 72 after the surgery. The outcomes observed in every study patient was almost outstanding consistent with the literature. The preoperative and postoperative results were statistically significantly different.

The subacromial distance was measured using radiological means in our study. Prior to the surgery, the mean subacromial distance was approximately 10.3 mm in the intact shoulder and 9.3 mm in the damaged shoulder. After the operation, it increased to a mean of 10.9 mm approximately. The shorter subacromial distance in the diseased shoulder before the surgery, compared to the intact one, can be explained with the following factors including the diminished depressing strength of the supraspinatus muscle, the intra-articular narrowing caused by the inactivity due to pain, the presence of osteoarthrosis in the older age patients, and the emergent hypertrophic spurs in the acromioclavicular joint. Subacromial decompression and debridement, as well as the application of pressurized water into the intra-articular space during the arthroscopy cause significant increases in these distances. The current study suggests that a subacromial distance less than 9.3 mm can be recognized as an important criterion in making the diagnosis of SIS.

Shoulder arthroscopy is becoming increasingly common today and the success of this procedure will be likely if potential complications are avoided. Neurologic complications are among the most frequent complications with rates ranging between 0 and 30% (21). They may emerge depending on the way of entry, occurring as traction injuries, or they may develop according to the position of the patient (22). The involved peripheral nerves may include the axillary nerve, median nerve, radial nerve, ulnar nerve, and the musculocutaneous nerve (21). Many of these injuries occur in the form of neurapraxia and almost all of them resolve over time. Nerve injuries may develop during the placement of the portals if optimal care is not exercised. Another common complication during shoulder arthroscopy is the emergent increased compartment pressure due to the leakage of lavage fluid out of the joint capsule into the surrounding tissues. Ogilvie-Harris and Boynton performed arthroscopic acromioplasties in 25 patients and reported that the mean pressure on the deltoid muscle was 27 mmHg and 72 mmHg during the glenohumeral arthroscopy and subacromial arthroscopy respectively. They added that the pressure returned to the normal levels in the 4th minute after the arthroscopy although the oedema in the muscle persisted further. The authors found normal results in the electromyography in the postoperative 4th and 6th weeks (23). The studies conducted by Lee et al. (24) also support these results. The rates of infection after the shoulder arthroscopy is quite low and most centres do not use prophylactic antibiotics at all. The rates of infection have been reported in the range from 0.04% to 0.23% in large series (25). Iatrogenic cartilage injuries are not occasional, which may develop accidentally during the placement of the portals. However, long term outcomes of these injuries have not been reported. The relatively rare complications of shoulder arthroscopy may include deep vein thrombosis, subcutaneous emphysema, pneumomediastinum, and pneumothorax. In our study, some complications developed in the study patients, too, including biceps tendinitis in 8 (10%) patients, triceps tendinitis in 2 (5%) patients and neuropraxia in 4 (10%) patients. Corticosteroids injections were made in 2 patients with biceps tendinitis. The complications did not persist in any of the patients as observed in the 8th week follow-up visits after physical therapy.

Conclusion

The subacromial distance should be recognised as an important criterion in the diagnosis of SIS and should be compared to that of the opposite shoulder. In patients with Stage 3 SIS and Stage 2 SIS who do not respond to the conservative treatment modalities, the arthroscopic subacromial decompression have been suggested to be an effective treatment option in recent years, in terms of reducing the pain, returning to the daily activities of living, and increasing the range of motion in the shoulder. The following factors in the medical histories of the patients with SIS, including chronic diseases and previous traumas does not affect the outcome of the treatment. As a result of this study, it has been determined that when used in combination with the support of functional and radiological data of the respective patients, the arthroscopic subacromial decompression surgery is an effective method for the treatment of SIS.

Ethics

Ethics Committee Approval: This study was aprroved by the Atatürk University Institutional Review Board (decision date and no: 12.06.2009-5/195).

Informed Consent: All volunteer patients included in this study were verbally informed about the study protocol and they signed the informed consent form.

Peer-rewiev: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: V.Y., Ö.S.Y., Concept: V.Y., Ö.S.Y., Design: V.Y., Ö.S.Y., Data Collection or Processing: V.Y., Analysis or Interpretation: V.Y., Ö.S.Y., Literature Search: V.Y., Writing: V.Y.

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Case Report / Olgu Sunumu

Repair of a Partial Anomalous Pulmonary Venous Connection After Mitral Valve Replacement: A Case Report

Mitral Kapak Replasmanı Sonrası Kısmi Pulmoner Venöz Dönüş Anomalisinin Tamiri: Olgu Sunumu Kısmi Pulmoner Venöz Dönüş Anomalisi

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Abstract

Partial anomalous pulmonary venous connection (PAPVC) is a rare congenital disorder with an incidence 0.5% of all congenital cardiac defects. Usually seen with congenital cardiac defects such as sinus venosus type interatrial septal defects or patent foramen ovale. Patients are asymptomatic until later in life (usually not hemodynamically significant and it is usually well tolerated by patients) and incidentally diagnosed with routine chest film, central catheter misplacement or post mortem examinations. In open hearts surgeries appropriate preoperative diagnosis is crucial for the accompanying congenital heart defects. We report a case of a surgical treatment of PAPVC in a 56 year old woman who had a history of mitral valve replacement surgery 1 year ago.

Öz

Parsiyel pulmoner venöz dönüş anomalisi (PAPVC) nadir görülen bir konjenital hastalıktır. Tüm konjenital kalp kusurları içinde insidans %0,5'dir. Genellikle bu tür doğumsal kalp kusurları sinüs venosus tipi atriyal septal defekt veya patent foramen ovale ile birlikte görülmektedir. Hastalar hayatlarının sonraki dönemlerine kadar asemptomatik olabilmekte (genellikle hemodinamik olarak anlamlı olmayan ve genellikle iyi tolere edilen) ve tesadüfen akciğer filmi, santral venöz kateterin yanlış yerleştirilmesi sonrasında veya otopsi sırasında tanı konulabilmektedir. Açık kalp ameliyatları öncesinde eşlik eden konjenital kalp defektlerinin tanısı çok önemlidir. Biz 1 yıl önce mitral kapak replasmanı ameliyatı öyküsü olan PAPVC tanısı alan 56 yaşındaki kadın hastanın cerrahi tedavisini sunduk.

Keywords
Partial anomalous pulmonary venous connection, surgical treatment, diagnosis

Anahtar Kelimeler
Parsiyel pulmoner venöz dönüş anomalisi, cerrahi tedavi, tanı

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Introduction

Partial anomalous pulmonary venous connection (PAPVC) is a rare congenital disorder with an incidence 0.5% of all congenital cardiac defects. One to three of the pulmonary veins (PV) drains oxygenated blood into the right atrium (RA) instead of the left atrium (LA) through the innominate vein (IV), superior vena cava (SVC), inferior vena cava (IVC), vena azygos or coronary sinus. Persistent left SVC is the most common cause with an incidence of 4.5% (1,2). Usually seen with congenital cardiac defects such as sinus venosus type atrial septal defect (ASD) or patent foramen ovale (sinus venosus type ASD are usually corrected by baffled patch closing). Isolated PAPVC without any other abnormality is very rare (3,4). Patients are asymptomatic until later in life (usually not hemodynamically significant and it is usually well tolerated by patients) and incidentally diagnosed with routine chest film, central catheter misplacement or post mortem examinations. Computed tomography (CT) scanning, magnetic resonance (MR), venography and catheterization of the pulmonary artery are used for diagnosing. We describe the surgical technique of reimplantation of the left SPV into the LA in a patients with PAPVC to the IV via a vertical vein without ASD with a history of (mitral valve repair) MVR surgery.

Case Report

Fifty-six year-old woman admitted our hospital with continuing complaints of dyspnea [New York Heart Association (NYHA) class 2], fatigue and palpitation after exercise for 10 months. She had a history of MVR surgery (2013), hypertension, diabetes and dyslipidemia. Physical examinations showed pretibial edema, venous distension and hepatojuguler reflux. The heart rate was 85 bpm and sinus rhythm in electrocardiogram. The blood pressure was 125/75 mmHg. First heart sound normal, second heart sound was harsh. Peripherical pulses were normal. Laboratory tests were within normal limits. The chest X-ray showed enlarged pulmonary arteries and increased pulmonary vascularity with a double density sign on the left paratracheal area. The transthoracic and transesophageal echocardiography [Transesophageal echocardiography (TEE)] were performed. Normal left ventricle, severely dilatation on the right heart chambers and severe pulmonary hypertension (PH) was found. There was no shunt on the atrial septum. A cardiac catheterization was performed, severe PH (mean pulmonary artery pressure 50 mmHg) and any significant findings in the coronary bed was detected. On computed tomography (CT) scan of the thorax showed a PAPVC with drainage of the left upper PV into the IV via a vertical vein (Figure 1). Based on these findings we decided to perform redo surgery. After cannulation of the right common femoral artery and vein patient was connected to the heart-lung machine then median sternotomy was performed, exploration was made with blunt and sharp dissection. After switching to bicaval venous cannulation, a clamp was placed on the ascending aorta. Subsequently a single dose of antegrade isotermic blood cardioplegia was administered to arrest the heart. Cardiopulmonary bypass (CPB) was performed with moderate hypothermia. The anomalous PV with vertical vein, SVC, left IV were dissected and encircled (Figure 2). The anomalous vein was ligated at the junction of the IV to facilitate the repositioning. Due to the left atrial appendix had been ligated for atrial fibrillation prior to the MVR surgery, partial clamp was placed in the left atrial wall. Longitudinal incision was made in the LA. Using a 10 mm Dacron greft anastomosis was performed between the left SPV and the LA (Figure 3). The patient was weaned off CPB with appropriate inotropic support.

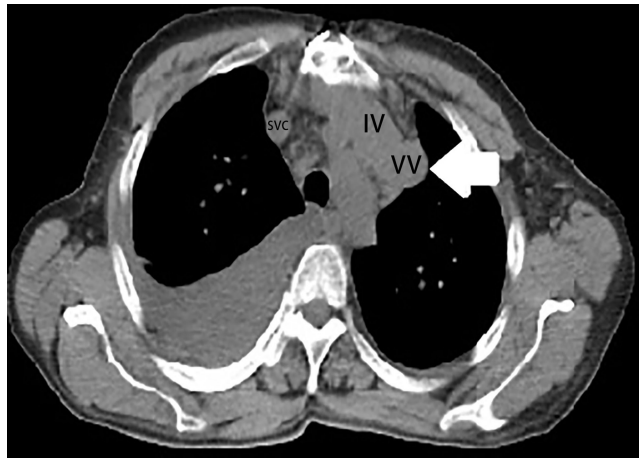

Figure 1. Partial anomalous pulmonary venous connection with drainage of the left superior pulmonary vein into the innominate vein via a vertical vein (arrow) and superior vena cava on computerized tomography scan

Discussion

PAPVC is a rare congenital anomaly and usually clinically silent that one or more PV drain into a systemic vein such as SVC, IVC, azygos vein, IV or directly to the RA rather than the LA since the early embryonic period. The incidence of PAPVC is 0.4-0.7% in total population. 10% are left sided and in 3% there is a connection between left lung and the left brachiocephalic vein. In 80-90% of patients are presented with an ASD (85% are sinus venosus type and 10-15% are secundum type). The severity of symptoms and complications depend on the shunt flow and extent of the left-right short circuit and the presence of other cardiac or pulmonary abnormalities (5). Diagnosis is made by echocardiography, computed tomography angiography, magnetic resonance imaging or cardiac catheterization and also pulmonary angiography provides a more detailed image. In this case, the anomalous venous return was not diagnosed by TEE on the prior MVR surgery. On account of continuing complaints of dyspnea (NYHA class 2), fatigue and palpitation after exercise for 10 months we decided to repeat both transthoracic and TEE. Unfortunately no anomalous was detected except severe PH, then chest CT angiography and cardiac catheterization was performed.

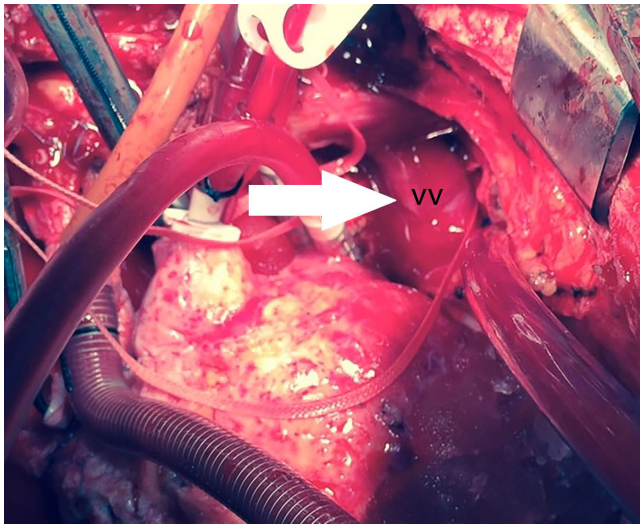

Figure 2. Externel view of the vertical vein (arrow)

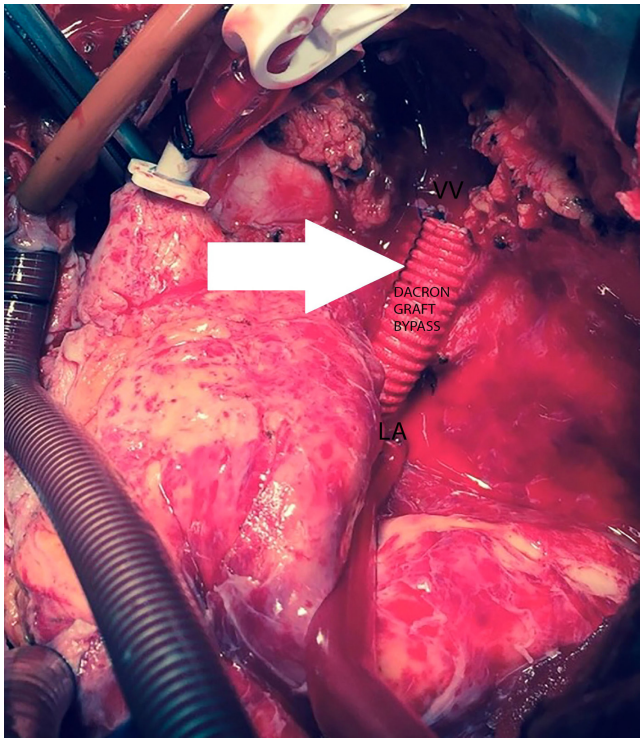

Figure 3. Intraoperative image. Interposition of dacron graft between innominat vein and the left atrium (arrow)

In 42.8% of patients are presented with PH. Besides, some authors determined that using echocardiography may fail in diagnosing due to outflow of all PV to the LA can not be differentiated (6). PAPVC can cause hemodynamically significant right to left shunt (Qp: Qs N 1.5:1), right ventricular failure or pulmonary vascular obstructive disease therefore, this identity must be treated surgically. Surgical treatment results of PAPVC surgery are generally good (7). Timing of the surgery is essential.

In conclusion, in open hearts surgeries appropriate preoperative diagnosis is crucial for the accompanying congenital heart defects. During open heart surgery PV's are not investigated routinely by surgeons whether there is a congenital defect or not. On account of this cardiologists should be more skeptical for overlooked congenital heart defects. On the other hand timing of cardiac surgery is essential to prevent right heart failure and improve patient's quality of life.

Ethics

Informed Consent: We received indormed consent from the patient.

Peer-review: Internally peer-reviewed.

Authorship Contributions

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

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