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Contact

Editorial Office
Address for Correspondence
Selimiye Mah. Tıbbiye Cad. 34668 Üsküdar, İstanbul/Turkey
Phone: +90 216 418 96 16
E-mail: tipfakultesi@sbu.edu.tr

Publisher/Issuing Body

Galenos Yayınevi Tic. Ltd. Şti.
Molla Gürani Mah. Kaçamak Sok. No: 21, 34093, Fındıkzade, İstanbul, Turkiye
Phone: +90 212 621 99 25
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REVIEW

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Cerebral Palsy: An Overview

Serebral Palsi: Genel Bakış

Koza Duman

Dr. Ayten Bozkaya Spastic Children's Hospital and Rehabilitation Center, Clinic of Physical Medicine and Rehabilitation, Bursa, Turkey

ABSTRACT

Cerebral palsy (CP), the most common cause of disability in childhood, was first described in 1861 by the English orthopedist William Little. CP, which has been expressed in different forms for many years, has been defined in 2006 by an international consensus as "a group of permanent disorders of the development of movement and posture, causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing or fetal brain". CP still remains the most common cause of childhood disability with a prevalence of 1.7-3.1 per 1.000 live births. Today, there are increasing publications stating that risk factors in the aetiology of CP can be traced back to pre-conception period. However, when risk factors considered, prenatal factors appear as the main cause with a weighted rate of 75%. As our knowledge on etiology mounted up, studies on prevention procedures also accelerated. CP is a clinical diagnosis. Therefore, being alert for risk factors is the first and most important step. CP treatment is planned with an integrative approach together with rehabilitation exercises, medical and surgical treatments. The main goal of programs are to enable children to reach their maximum capacity. Despite the technological advances in medical diagnosis and treatment protocols, CP remains to be the most common cause of paediatric disability in childhood. Considering aspects like risk factors, aetiology, prevention measures, diagnosis and management; there are many questions that need answers.

Keywords: Cerebral palsy, diagnosis, management, risk factors, botulinum toxin A, rehabilitation

ÖZ

Çocukluk çağının en sık görülen disabilite nedeni olan serebral palsi (CP) ilk kez 1861 yılında İngiliz ortopedist William Little tarafından tanımlanmıştır. Uzun yıllar boyunca farklı biçimlerde ifade edilerek günümüze ulaşan CP tanısı, 2006 yılında uluslararası bir konsensüs ile "gelişmekte olan fetal veya infant beyin dokusunda sabit hasar sonrası görülen ve aktivite sınırlaması ile sonuçlanan, postür ve hareketin normal gelişiminde duraksamaya yol açan kalıcı bozukluklar grubu" olarak tanımlanmıştır. CP günümüzde her 1,000 canlı doğumda 1,7-3,1 prevalans ile hala en sık görülen çocukluk dönemi disabilite nedeni olmaya devam etmektedir. Bu rakam ülkenin gelişmişlik düzeyi arttıkça düşmektedir. Günümüzde CP etiyolojisinde risk faktörlerinin konsepsiyon öncesine dek uzanabildiğini söyleyen yayınlar artmaktadır. Bununla birlikte; ana neden olarak prenatal faktörler %75 gibi ağırlıklı bir oran ile karşımıza çıkmaktadır. Etiyoloji hakkında bilgilerimiz arttıkça korunma prosedürleri üzerine çalışmalar artmaya başlamıştır. CP klinik bir tanıdır. Bu nedenle risk faktörleri açısından alert olmak ilk ve en önemli adımdır CP tedavisi rehabilitasyon uygulamaları, medikal ve cerrahi tedaviler ile birlikte bütünleyici bir yaklaşımla planlanır. Tedavide temel hedef fonksiyonelliği artırarak çocukları sosyal hayata entegre edebildiğimiz maksimum kapasitelerine ulaşmalarını sağlamaktır. Tıbbi tanı ve tedavilerdeki tüm teknolojik ilerlemeye rağmen CP prevalansı beklenen azalmayı göstermemektedir. Bu nedenle risk faktörleri, etiyoloji, önleyici yaklaşımlar, teşhis ve tedavi gibi unsurları göz önüne alındığında; cevaplanması gereken birçok soru olduğu akılda tutulmalıdır.

Anahtar Kelimeler: Serebral palsi, tanı, tedavi, risk faktörleri, botulinum toksin A, rehabilitasyon

Introduction

Cerebral palsy (CP), is not a defined, separate disease classification, but an umbrella term. The term was first described in 1861 by the English orthopedist William Little. Little has correlated a difficult labour and neonatal hypoxia with limb spasticity and consequential musculoskeletal deformities (1). Although it was first described as a sequela of difficult postpartum hypoxia, we now know that this observation explains a very limited group. CP, which has been expressed in different forms for many years, has been defined in 2006 by an international consensus as "a group

Address for Correspondence: Koza Duman, Dr. Ayten Bozkaya Spastic Children's Hospital and Rehabilitation Center, Clinic of Physical Medicine and Rehabilitation, Bursa, Turkey

Phone: +90 224 216 00 66 E-mail: kozaaydoseli@gmail.com **ORCID ID:** orcid.org/0000-0002-3567-6823

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of permanent disorders of the development of movement and posture, causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing or fetal brain" (2).

Today, CP still remains as the most common cause of childhood disability with a prevalence of 1.7-3.1 per 1.000 live births. The figure decreases as the development level of the country increases (3,4).

Etiology and Risk Factors

For more than 100 years, the main etiology of CP was believed to be prolonged labour. The outcome was tried to be explained by relating it to hypoxia during or after birth. However, despite significant improvements in medical facilities, birth comfort and postpartum care; over the years the incidence of CP did not decrease as expected (5). Due to this fact, researchers keep conducting epidemiological studies worldwide.

Considering risk factors, it should be kept in mind that not every baby with risk factors results in diagnosis of CP. Data certifies that, approximately 55% of children diagnosed with CP before the age of 1 years did not meet the diagnostic criteria at the age of 7 years (6).

Today, there are increasing publications stating that risk factors in the aetiology of CP can be traced back to pre-conception period. Studies indicate that even maternal sociodemographic characteristics and reproductive history are associated with CP (7,8). However, when risk factors considered, prenatal factors appear as the main cause with a weighted rate of 75%. This figure is followed by risk factors of infantile and neonatal periods with 10% and 18%, respectively (5,9).

Studies have shown that the frequency of defects in brain development are correlated with gestational week. Gestational week (<32 weeks) and birth weight (<2.500 g) and incidence of damage are inversely related to each other (10,11,12).

Prevention

As our knowledge on etiology mounted up, studies on prevention procedures also accelerated.

Therapeutic hypothermia: Therapeutic hypothermia applications within 6 hours of birth is aimed to prevent ischemic damage by inhibition of inflammatory cascades and apoptotic cellular processes. It has been estimated that 1 out of 8 new-borns to whom this method is applied is prevented from developing CP symptoms (13,14).

Caffeine: Caffeine is also an agent in trial as a prevention measure. Caffeine for apnea of prematurity trial results indicates caffeine reduces the incidence of CP in very low-birth-weight infants (13,15).

Corticosteroids: When steroid administrations are considered adverse data due to administration time is available. Literature dictates warnings for the use of steroids for the prenatal and postnatal period. While the prenatal betamethasone administration in preterm infants is found to reduce the PVL, early (<8 days) postnatal steroid administration is associated with an increase in CP numbers, despite the pulmonary benefits. In 2010, the American Academy of Paediatrics made recommendations to limit the use of postnatal corticosteroids (13,16,17,18).

Magnesium: Administration of magnesium sulfate during the antenatal period is important for neuroprotection in preterm infants. Magnesium sulfate reduces inflammatory effects through pro-inflammatory cytokine suppression. However, the results are varying for obese mothers. It is wise to state that there is no consensus on the results of the application (13,19).

Clinical Features

CP is a clinical diagnosis. Being alert for risk factors is the first and most important step. Early diagnosis and planning treatment without losing time are of vital importance for these children, to reach the highest physical and cognitive level they can be. The correlation between Paediatricians and Physical Medicine and Rehabilitation (PMR) professionals is one of the most important components of this process. Directing risky babies to PMR specialists as soon as possible will prevent delays in diagnosis and treatment plan (20,21).

The compatibility of motor development with chronological age, persistent primitive reflexes and delay in voluntary motor control are important in terms of diagnosis in infants with prenatal, perinatal and postnatal risk factors. However, considering that spasticity is not fully established before 6 months, athetoid movements are not evident until the age of two, and persistent Babinsky reflexes are not significant, it is difficult to make a definitive diagnosis before the age of two (22,23,24). Therefore, every suspected baby should be included in a rehabilitation program without losing time. MRI and laboratory tests to support the neurological evaluation will accelerate the diagnosis process. As in every other subject, differential diagnosis is also crucial in this aspect. It is possible to reach the final result after excluding progressive neurological diseases, metabolic and genetic disorders. Based on the information above The European Database Group (SCPE) has accepted the optimal age as 5 to confirm the diagnosis (25).

Classification: Clinically, CP can be classified by different methods. According to the extremity involvement, the terms hemiplegia, diplegia, tetraplegia is used; According to the dominant tone disorder, it can be defined as spastic, dyskinetic and ataxic. Balf and Ingram (26), Hagberg et al.

(27) and SCPE (2006) (25) classifications are available as facilitating tools (Table 1). When predominant symptoms are considered, spastic CP is the most common type of CP with a rate of 70-80%. It is presented with increased deep tendon reflexes, pathological Babinsky response and upper motor neuron syndrome symptoms. When ambulant patients are considered scissoring gait and toe walking are common clinical features due to internally rotated and adducted hips and gastrocnemius spasticity. Dyskinetic or athetoid CP (10-20%) which characterized by abnormally slow, writhing movements of the hands, feet, arms or legs that are exacerbated during periods of stress absent during sleep. The rarest type is ataxic CP (5-10%) which impairs balance and coordination. Wide base gait at ambulation and intentional tremors are presented as main characteristics. In the case of mixed symptoms, SCPE suggestions is that the classification should be done on the basis of the predominant symptoms (9,25,28).

Co-morbidities: Different co-morbidities accompanying motor deficits can be seen in children with a diagnosis of CP. Epilepsy (15-90%), mental retardation (40-65%), speech problems (50%), urinary incontinence (30%), malnutrition and growth retardation (27%), and drooling (10%) are the most common symptoms. To achieve desired goals, rehabilitation plans should be done with co-morbidities taken in consideration (6,28,29,30,31,32,33,34,35).

Management

Non-surgical methods: The aim in the rehabilitation of CP is to provide the child with the optimum function that he/she can perform with his/her existing neuromotor capacity and to either reduce existing complications or prevent possible complications. Therefore, each rehabilitation plan is an individually tailored program for each patient.

Rehabilitation is based on term "neuroplasticity". A term that is used to explain the ability of the nervous system to undergo permanent structural and functional changes in reaction to internal and external stimuli. It works in the case of both a damaged and undamaged brain, which "learns anew" as the result of rehabilitation. The greatest possibilities of modification occur at the earliest stages of development of the central nervous system. It is at this stage that the brain demonstrates a high degree of plasticity, which favours the compensation of various deficiencies. Since the neuroplasticity potential is higher in the early stages of life,

Table 1. Classification of CP by Balf and Ingram (26) and SPCE

Ingram's classification	
Type	**Definition**
Diplegia	Spastic paresis occurs especially in lower limbs, 3 or 4 limbs (including quadriparesis syndromes with prevailing lower limb paresis over upper limb paresis).
Hemiplegia	Spastic paresis is unilateral (right or left sided) with predominance of upper or lower limb.
Bilateral hemiplegia (tetraplegia)	Spastic tetraparesis with predominance of upper limb paresis (most severe type of CP in terms of severity of motor disability and co-existing problems).
Ataxia	Muscle tension is reduced, accompanied by hand-eye coordination disorders. Bilateral or with the predominance of one side of the body.
Dyskinesia	Dystonic, athetosic, choreic type of CP, accompanied by trembling or manifesting itself in frequent changes of muscle tone.
Mixed types	The above mentioned types in various combinations.
SCPE classification	
Type	**Definition**
Spastic type	Characterized by enhanced muscle tension, hyperreflexia and pathological reflexes: Split into unilateral spastic and bilateral spastic, without further division into diplegia, tri- or tetraplegia.
Dyskinetic type	Patients perform involuntary, uncontrolled, repetitive, sometimes stereotypical movements; muscle tension, which can be both increased or decreased, and frequently changes over time. The following are identified by SCPE: - Dystonic CP with a predominant faulty posture and enhanced muscle tension (so-called hypertonic-hypokinetic). - Choreoathetotic CP: this type is characterized by quick, uncontrolled, violent, frequently "fragmenting" movements which overlap slow, constantly changing "twisting" movements; tension is usually changeable, predominantly lowered (so-called hypotonic-hyperkinetic).
Ataxic type	Related to motor coordination loss, which results in ataxia, movement smoothness, and trembling; in this type of CP lowered muscle tension is predominant.
CP: Cerebral palsy, SPCE: Surveillence of cerebral palsy in Europe	

it is important to start the treatment of children with CP in the earliest possible period (20,21).

CP management is an integrative approach together with rehabilitation applications, physical therapy modalities, medical and surgical treatments. The main goal in management is to control spasticity, avoid involuntary movements, preserve range of motion, increase function, and enable children to reach their maximum capacity that we can integrate into social life (36).

In rehabilitation programs, neuro-rehabilitative treatment approaches (Bobath, Vojta) form the basis of treatment. Supporting rehabilitation exercises with other modalities such as occupational therapy and speech therapy, and integrating professionals such as psychologists and social workers to the program positively effects the quality and outcome of the treatment. Optimal outcomes require a team approach.

Although it is predicted that intensive treatment programs will lead to more satisfactory results, there is no consensus on the threshold for intensity and duration of rehabilitation programs (37). Analysing rehabilitation programs; it will be noticed that there is no consensus on content, outcomes or long-term gains (38,39,40,41,42,43,44). The reason for the lack of consensus on the results may be attributed to complex clinical feature of the diagnosis and individually tailored nature of the treatment programs. This significant cause result in difficulty in randomization and obtaining the outcomes as numerical data.

Modalities as bracing, kinesiotape, biofeedback and neuromuscular electrical stimulation (NMES) are integral parts of the rehabilitation program.

Bracing: Orthoses prescribed mainly for two different purposes; to prevent deformities and to increase function (45).

Kinesiotape: Kinesiotape was introduced in 1996 by Kenzo Kase to control pain, regulate muscle tone, increase muscle strength, and regulate blood and lymph flow. They are used to increase muscle strength, posture control and spasticity control in the treatment of CP (46).

Biofeedback: Biofeedback application is used to train a single muscle activity in static positions in patients without cooperation deficit. The clinical application of biofeedback to improve a patient's motor control begins by re-educating that muscle by providing visual or audio feedback of electromyogram, positional or force parameters in real time (47,48).

NMES: NMES is an adjuvant treatment for muscle strengthening and spasticity control, which has been shown to improve motor function in CP treatment programs. Similar to rehabilitation programs, there is no consensus on the intensity, duration and contribution of NMES to treatment outcomes (49).

Botulinum toxin: Botulinum toxin type-A (BoNT-A) is a dose-dependent and reversible agent that blocks presynaptic acetylcholine release at the neuromuscular junction. With the increase in clinical experience in recent years, the agent has become the most widely used medical intervention in children with CP. The evidence is that with the appropriate use of BoNT-A in younger children the onset of fixed equinus might be delayed to a small but important degree, permitting later utilization of orthopaedic surgery at optimum age. This means reduction in the serial operations that children used to be exposed between the ages of 2-8 and "birthday syndrome" has become an out of date term. However, the optimism regarding the prevention of contractures generated by the spastic mouse study has never been translated to the clinical practice and almost all of the children still need release surgery. In the case of in non-ambulatory children Botulinum toxin administration is recommended only for pain relief. The agent has the power of increasing the quality of life with the right patient selection. However, there is still no consensus among practitioners on issues such as treatment protocols and application frequency (50,51,52,53,54,55,56,57,58).

Surgical Interventions

Selective dorsal rhizotomy (SDR): SDR is a surgical method that is performed by the incision of the posterior nerve roots. Surgery is applied for spasticity management. The most appropriate age range for CP patients has been determined as 4-6 years. Although undesirable results such as post-operative deep sensory loss, urinary retention, hypotonia and persistent low back pain have been reported, it is an effective surgical method with satisfactory results with the right case selection in lower extremity spasticity (59).

Orthopaedic surgical interventions: Orthopaedic surgical interventions (release surgery, osteotomy, tendon transferring techniques) which are widely performed in the treatment of CP, are applied with the aim of preventing deformities and correcting the existing deformity. For surgical interventions, it would be appropriate to wait until the age of 6 when the child's gait pattern matures. The important aspect to keep in mind is the principle of "performing simultaneous multi-level release surgery in one session". It has been reported that the morbidity of a single session surgical approach is lower compared to multisession surgical approach. When this principle is applied, it has been observed that the results of post-op rehabilitation outcomes are more satisfactory, and the gains

at postural and functional improvements are longer lasting (6,36,60,61).

Conclusion

Despite the technological advances in medical diagnosis and treatment protocols, CP remains to be the most common cause of paediatric disability in childhood. Considering aspects like risk factors, etiology, prevention measures, diagnosis and management; there are many questions that need answers.

Ethics

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Burnout Effects of Workplace Violence on Health Workers

İş Yeri Şiddetinin Sağlık Çalışanları Üzerindeki Tükenmişlik Etkileri

Başak Çap[1], Zeynep Korkut[1], Mihriban Çalışkan[1], Nur Besra Baştuğ[1], Ömer Seyfi Ekinci[1], Kürşad Nuri Baydili[2], Halide Nur Ürer[3]

[1]*University of Health Sciences Turkey Hamidiye Faculty of Medicine, İstanbul, Turkey*

[2]*University of Health Sciences Turkey Faculty of Medicine, Department of Biostatistics and Medical Informatics, İstanbul, Turkey*

[3]*Yedikule Chest Diseases and Chest Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey*

ABSTRACT

Background: Violence against health workers; it is a condition that causes unfavourable effects in many areas such as social, emotional, psychological and quality of service.The aim of the study is to determine the risks of workplace violence and the effects of post-traumatic burnout in the victim of health workers by evaluating the awareness of violence.

Materials and Methods: The research was carried out with physicians and nurses working in public institutions affiliated with the Ministry of Health. The survey method was used in the study. The survey consisted of three basic sections and had a total of 37 questions. Demographic information in the first part; in the second part, the nature of the violence, the reporting of post-traumatic violence and the status of receiving professional support were questioned. In the last section, Maslach burnout inventory was included. The questionnaire was communicated to workers via their social media accounts and networks. The data was analyzed with SPSS 25 package program.

Results: Four houndred-fifteen health workers participated in the study. 86.9% percent of respondents said they had been exposed to violence. After the violence, 36% of employees complained and 7% received professional support. Emotional exhaustion and depersonalization were found to be significantly higher ($p<0.001$) in health workers who were exposed to violence. As the age increased, scores of emotional exhaustion and depersonalization decreased and personal achievement scores increased. The emergency department was the most at risk group of burnout levels among clinical units.

Conclusion: Health workers are highly exposed to workplace violence. As a result, depersonalization and emotional exhaustion occur and their personal success decreases. Especially young age group health workers and emergency clinics are in the high-risk group. Awareness, sensitivity and effectiveness of the fighting violence at legal and social level should be increased. Pre-graduation medical education should also be evaluated in this context.

Keywords: Workplace violence, health personnel, burnout

ÖZ

Amaç: Sağlık çalışanlarına yönelik şiddet; sosyal, duygusal, psikolojik ve hizmet kalitesi gibi pek çok alanda olumsuz etkiler bırakan bir durumdur. Çalışmanın amacı; iş yeri şiddetinin risklerini ve şiddet farkındalığını değerlendirerek mağdur sağlık çalışanlarında travma sonrası tükenmişliğin etkilerini saptamaktır.

Gereç ve Yöntemler: Araştırma Sağlık Başkanlığı'na bağlı kamu kurumlarında çalışan hekim ve hemşirelerle yürütüldü. Çalışmada anket yöntemi kullanıldı. Üç temel bölümden oluşan ankette, toplam 37 adet soru bulunmaktaydı. İlk bölümde demografik bilgiler; ikinci bölümde şiddetin niteliği, travma sonrası şiddeti bildirme ve profesyonel destek alma durumları; son bölümde Maslach tükenmişlik envanteri yer aldı. Soru formu, çalışanlara sosyal medya hesapları ve ağları üzerinden iletildi. Veriler SPSS 25 paket programı ile analiz edildi.

Bulgular: Çalışmaya 415 sağlık çalışanı katıldı. Katılımcıların %87'si şiddete maruz kaldığını belirtti. Şiddet sonrası çalışanların %36'sı şikayette bulundu, %7'si profesyonel destek aldı. Şiddete maruz kalmış sağlık çalışanlarında duygusal tükenme ve duyarsızlaşma anlamlı oranda yüksek ($p<0,001$) bulundu. Yaş arttıkça duygusal tükenme ve duyarsızlaşma puanları düşmekte, kişisel başarı puanı ise artmaktaydı. Acil servis, klinik birimler içinde tükenmişlik boyutlarında en riskli grup idi.

Address for Correspondence: Başak Çap, University of Health Sciences Turkey Hamidiye Faculty of Medicine, İstanbul, Turkey
Phone: +90 536 973 24 67 E-mail: basakcapp@gmail.com **ORCID ID:** orcid.org/0000-0003-3063-404X
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ÖZ

Sonuç: Sağlık çalışanları, iş yeri şiddetine yüksek oranda maruz kalmaktadır. Bunun sonucunda duyarsızlaşma ve duygusal tükenme meydana gelmekte, kişisel başarıları düşmektedir. Özellikle genç yaş grubu sağlık çalışanları ve acil klinikler riskli grupta yer almaktadır. Şiddete karşı farkındalık, duyarlılık, şiddetle mücadelenin yasal ve toplumsal düzeyde etkinliği artırılmalı; mezuniyet öncesi tıp eğitimi de bu kapsamda değerlendirilmelidir.

Anahtar Kelimeler: İş yeri şiddeti, sağlık çalışanı, tükenmişlik

Introduction

The World Health Organization (WHO) implies violence as the intentional use of force against a person or community with a high probability of resulting in injury, death, psychological harm or developmental disability.

In recent years, the increase of all kinds of violence in the world is remarkable. Workplace violence is one of them. It is defined as any act or threat of physical violence, harassment, intimidation or other threatening disruptive behavior that occurs at the work site. Workplace violence in health sector is psychological, physical, sexual, economic etc. abuses directed by the patient, their relatives or other individuals to health workers.

Unfortunately, violence in healthcare has become a very common phenomenon. WHO reported that 1/4 of workplace violence occurs in the health sector and more than 50% of workers are victims of violence (1,2). It is emphasized that attacks against healthcare workers are more common than guards and police (3). Surgical unit staff, nurses and general practitioners are the most exposed to violence in the sector (4).

As in other cases of violence, health providers are also negatively affected by violence. Victimization manifests itself in the workers with negative expressions and causing negativities in their social and professional life. These can have a physical, psychological, emotional, social and financial impact (5). Decrease in working efficiency, increase in burnout level and depersonalization are frequently observed.

Herbert Freudenberger implies burnout as a state of exhaustion in the internal resources of the individual as a result of wear and overload. However, depersonalization is an individual's unemotional behavior towards people (6).

Violence against health workers harms not only the victim but also the people around them and the system. It is a problem that concerns all segments of society. As medical students, we observe this and witness the increase in violence in healthcare day by day. This situation leads to our concerns about medicine and to question the choice of profession. The aim of the study is to review the risks of workplace violence and violence awareness and to determine the effects of post-traumatic burnout in victim employees.

Material and Methods

The research was carried out with physicians and that nurses work in public institutions affiliated with the university. The survey method was used in the study. It consisted of 3 sections with 37 questions. The first part included demographic information. These were gender, age range, marital status, worker's institution profile, occupation, clinical unit and status, clinical trial times. In the second part; whether there was violence, posttraumatic complaint and professional support, the nature of the violence (verbal, physical, time period which it occurs) was questioned. In the last section, Maslach burnout inventory was included. Turkish translation of inventory was used (7). Inventory alpha coefficient; it was 0.83 for emotional exhaustion, 0.63 for depersonalization and 0.72 for personal success. A five-point Likert scale was used to evaluate the questions.

The study was carried out on healthcare workers. Patients were not included in the sample. It was clearly stated in the survey that participation was optional. The introduction and survey form were created in an internet search engine system. Workers were communicated via social media accounts and networks. The survey was launched on The Google Forms system on January 25, 2021 and terminated on March 6, 2021.

Statistical Analysis

Data analysis was carried out using SPSS 25 package program. Frequency and percentage values were determined for qualitative variables.

Independent sample t-test was used in comparisons between qualitative variable categories containing two categories in terms of quantitative variables. One-Way ANOVA was used in comparisons between qualitative variable categories containing more than two categories in terms of quantitative variables. If there was a significant difference as a result of the One-Way ANOVA, the categories were compared in twos with the Tukey test. In the study, the p-value was considered significant if it was found to be less than 0.05.

Ethics committee approval was obtained in the study (University of Health Sciences Turkey Hamidiye Faculty of Medicine; 29.01.2021/5444), which oversees and includes patient consent.

Results

In total, 415 health workers completed the survey. The demographic information of the participants is shown in Table 1.

According to the profile of the health institution, 85.8% of the participants were working in the tertiary, 11.3% in the secondary and 2.9% in the primary health care institution. Internal medicine (21.9%) was the first in the distribution of physicians by clinical branch (Figure 1). Clinical distinction of nurses was not made.

In the physicians, 33 were general practitioners, 101 were assistants, 6 were chief assistants, 82 were specialists, 48 were associate professors and 41 were professors. The number of head nurses was 1 and the number of nurses was 103 (Figure 2).

It was determined that 361 (87%) health workers were exposed to violence. Types of violence and exposures were explained along with time periods (Figure 3). Five people were exposed to only physical violence during their working life. 3 people were exposed to only physical violence in the last 5 years.

To date, 81% of the workers exposed to violence were exposed to only verbal violence, 1.3% to only physical violence and 16.8% to both verbal and physical violence. In the last 5 years, 87.4% of the workers exposed to violence were exposed to verbal violence, 0.9% to physical violence, 11.6% to both verbal and physical violence. In verbal violence, 11.8% shouting, 11.5% hostile attitude, 10.5% swearing, humiliation, threats to life and complaining to higher authorities were detected. 66.1% of workers did not want to specify the nature of the violence. It was found that

Table 1. Demoghraphic information of participants

	n	%
Gender		
Female	263	63.4
Male	152	36.6
Age		
20-30 years	142	34.2
31-40 years	97	23.4
41-50 years	86	20.7
51 and older	90	21.7
Marital status		
Married	259	62.4
Single	156	37.6
Job		
Nurse	103	24.8
Doctor	312	75.2
Clinical work time		
Less than 1 year	57	13.7
1-5 years	166	40.0
6-10 years	50	12.0
More than 10 year	142	34.2

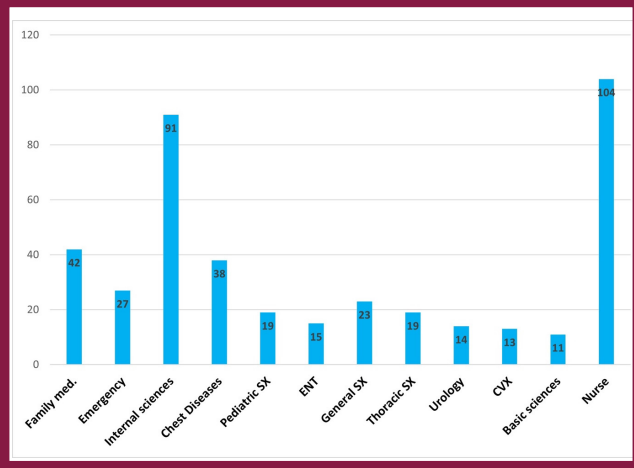

Figure 1. Distribution of workers by clinical branch. The majority of the participants in the study were internal medicine workers and nurses

SX: Surgery, ENT: Ear nose throat, CVX: Cardiovascular surgery

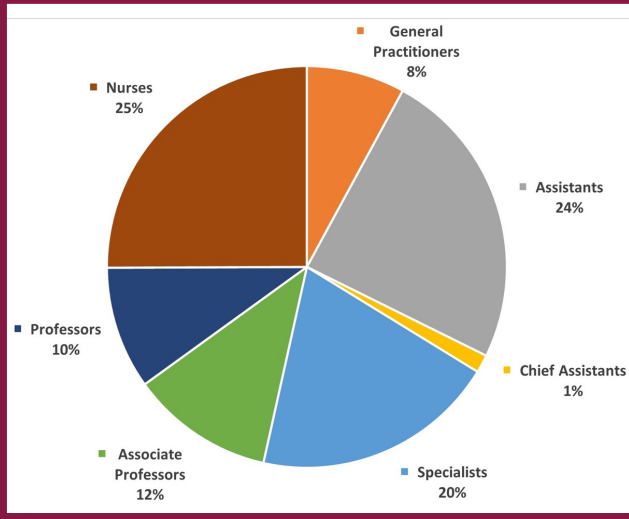

Figure 2. Status of participants. Most of the participants were nurses and assistant doctors

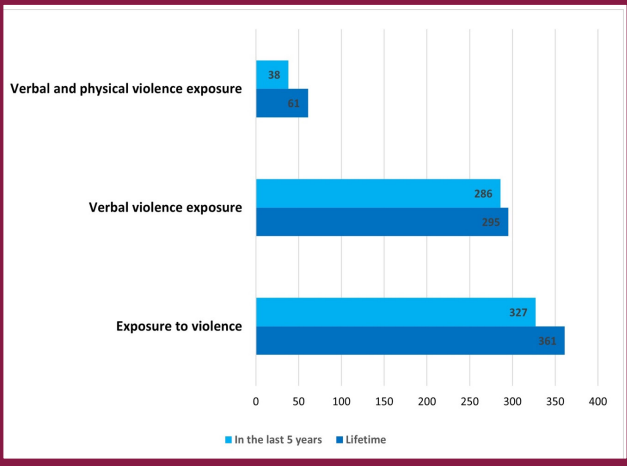

Figure 3. Violence victimization status in healthcare workers. High rates of exposure to violence were detected in the participants. The most common type of violence was verbal violence. When the exposure to violence was analyzed according to the time period, no results open to interpretation were found

86.3% of them who were exposed to physical violence were victims of manual assault and/or injury.

The rate of those who witnessed any violence in their working life was 80.5% in the last 5 years.

36.2% of the victims of violence reported that they made a complaint after the attack. 7.7% of the victims received professional support after the violence.

The results of Maslach emotional exhaustion, depersonalization and personal achievement sub-dimensions in healthcare workers are shown in Table 2.

Workers who were exposed to violence had higher scores of emotional exhaustion and depersonalization than those who were not exposed to violence.

Emotional exhaustion and depersonalization scores were significantly higher in the younger age group, emergency unit workers, unmarried workers and those who had served for five years or lessworkers. However, independently of each other; workers who met the criteria of advanced age, being married, working longer than 10 years and being a surgical unit staff had a significantly higher personal accomplishment score.

Significant differences in burnout sub-dimensions were found in violence exposure, exposure to violence in the last 5 years or before, age group, marital status, clinical working time, filing complaints, receiving professional support and clinical unit. The findings are listed in Table 3.

Discussion

The exposure rate of health workers to workplace violence in Turkey and around the world is in the range of 44.7-83.3% (8,9). In our study, the rate of 415 healthcare workers who were exposed to violence at least once in their lifetime was 87%.

The study found that despite a high rate of violent exposure, only 36.2% of victims reported it to the upper authority or initated legal action. The length or weariness of the complaint process may explain this. The high level of depersonalization scores of workers who have reported violence supports this. Additionally, the sense of revenge that may occur on the opposite side at the end of the process can be deterrent to reporting violence. However, perceiving violence as part of the profession may explain the tolerance of it (10,11,12,13).

Violence against health workers has negative effects in many important areas like social, emotional, psychological, socio-economic and quality of service (5,14). However, it is being suggested that the negative effects of violence are mostly manifested in psychological and emotional areas (5). Studies shows that health workers who violenced experience high rates of post-traumatic stress disorder, anxiety, discomfort, disappointment, lack of motivation, anxiety of being violent again and these effects extend to quit the job (15,16,17). Despite all this, small rate of workers apply for professional support (5). A parallel result was seen in the study. This is due to the victim's assessment of violence as a usual situation.

As showned by the research; workplace violence causes emotional burnout and depersonalization in health workers and reduces personal success of workers. Burnout caused by violence is the most important factor leading to both negative and positive defensive medicine (18).

Especially in young age group victims, the high rates of emotional burnout and depersonalization was remarkable. This is a result of relatively inexperienced health workers being at a bigger risk for violence (19). Decreased emotional exhaustion and depersonalization and increased personal achievement in the older group also support this (14,20). Older age group with more experience can be thought to manage stress better (4,14). Additionally, it can be said that the decrease in routine contact with patients in seniors reduces the risk of violence and therefore affects personal success positively.

Single health workers are reported to be more exhausted than married ones (20,21). The results of our study also support this. As a result, a family structure, which can share work-related stress and receive emotional support, affects workers positively.

Table 2. Maslach burnout sub-dimension scores in healthcare workers

Parameters	Emotional exhaustion	Depersonalization	Personal achievement
Exposure to violence			
No	1.22±0.72	0.57±0.72	3.19±0.68
Yes	**2.06±0.93**	**1.27±0.91**	3.03±0.56
Violence exposure in the last 5 years			
No	1.34±0.81	0.67±0.70	3.19±0.67
Yes	2.11±0.91	1.31±0.92	3.00±0.54
Violence exposure before the last 5 years			
No	2.00±0.94	1.22±0.93	3.03±0.57
Yes	1.50±0.87	0.77±0.66	3.20±0.63
Gender			
Female	2.11±0.86	1.20±0.86	3.01±0.56
Male	1.97±1.04	1.39±0.99	3.07±0.57
Age range			
20-30 years old	**2.39±0.77**	**1.63±0.92**	2.84±0.52
31-40 years old	2.05±0.97	1.27±0.95	2.96±0.55
41-50 years old	1.92±0.98	1.01±0.75	**3.17±0.56**
51 years and older	1.67±0.87	0.91±0.76	**3.25±0.52**
Marital status			
Married	1.96±0.89	1.12±0.81	**3.05±0.53**
Single	**2.23±0.96**	**1.52±1.01**	2.98±0.60
Profession			
Nurse	2.18±0.79	1.00±0.75	3.10±0.51
Doctor	2.02±0.96	1.35±0.94	3.00±0.57
Clinical trial time			
Less than 1 year	2.08±0.88	**1.46±0.82**	2.86±0.57
1-5 years	**2.27±0.92**	**1.51±1.00**	2.93±0.57
6-10 years	1.95±1.00	1.09±0.87	**3.07±0.50**
More than 10 years	1.82±0.86	0.96±0.71	**3.18±0.53**
Complaint status			
No complaints	2.00±0.90	1.18±0.89	3.02±0.54
Made a complaint	2.16±0.97	1.42±0.92	3.03±0.59
Professional support			
Did not apply	2.04±0.92	1.25±0.89	3.04±0.55
Applied	2.38±1.04	1.57±1.15	2.67±0.56
Clinical units			
Internal units	2.08±0.96	1.33±0.94	2.94±0.60
Emergency	**2.64±0.83**	**2.14±1.00**	2.88±0.46
Surgical units	1.67±0.86	1.13±0.75	**3.20±0.50**

Table 3. Maslach burnout subdivision p-values in healthcare workers

Parameters	p		
	Emotional exhaustion	Depersonalization	Personal achievement
Exposure to violence	**<0.001**	**<0.001**	0.058
Violence exposure for the last 5 years	**<0.001**	**<0.001**	0.017
Violence exposure before 5 years	**0.001**	**<0.001**	0.068
Gender	0.176	0.060	0.324
Age	**<0.001**	**<0.001**	**<0.001**
Marital status	**0.007**	**<0.001**	0.252
Profession	0.187	**0.001**	0.167
Clinical trial time	**0.001**	**<0.001**	**0.001**
Complaint status	0.111	**0.014**	0.859
Request for professional support	0.142	0.157	**0.008**
Clinical unit	**<0.001**	**<0.001**	**0.004**

It is known that women are more targets of violence than men (1,22). However, the study did not find any significant difference in the negative effects of violence, contrary to expectations. In this case, it should be discussed that violence does not recognize sexism.

Emotional exhaustion and depersonalization are higher in emergency room workers compared to other clinics; associated with their greater exposure to all forms of violence (4,15,23). Surgical units are the group with the lowest emotional exhaustion and depersonalization. Likewise, the group with the highest personal success is the surgical unit. However, in surgery, which is one of the places where violence is most common (15,24), workers burnout is expected to be higher. Their frequent encounters with workplace violence can help them manage pressure and stress better.

Study Limitations

There are some limitations in the research. The survey could not be carried out face-to-face due to the conditions of the lockdown of the Coronavirus disease-2019 pandemic. The online survey spread through the participants' social media accounts. Therefore, the true size of the research universe is unclear.

Conclusion

As a result, health workers are highly exposed to workplace violence. Consequently, depersonalization and emotional exhaustion occur and their personal success decreases. Especially, young age health and emergency workers are in the high-risk group. All forms of violence turns into a chronic progressive form that is difficult to deal with. Those who work to raise awareness, sensitivity and fight against violence should be encouraged. The fight against violence should include pre-graduation medical education as well as legal and social level.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained in the study (University of Health Sciences Turkey Hamidiye Faculty of Medicine; 29.01.2021/5444).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.B.B., Design: Ö.S.E., Data Collection or Processing: Z.K., Ö.S.E., Analysis or Interpretation: K.N.B., H.N.Ü., Literature Search: B.Ç., Z.K., M.Ç., N.B.B., Ö.S.E., Writing: B.Ç., Z.K., M.Ç., N.B.B., Ö.S.E., H.N.Ü.

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ORIGINAL ARTICLE

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The Role of Platelet Rich Plasma for Preventing Postoperative Peritoneal Adhesions in Adhesive Intestinal Obstruction in Rats

Ameliyat Sonrası İntestinal Obstrüksiyonu Olan Ratlarda Periton Yapışıklıklarının Önlenmesinde Trombositten Zengin Plazmanın Rolü

Gökhan Demirtaş[1], Pınar Celepli[2], Murat Kızılgün[3], Sema Hücümenoğlu[2], Hüseyin Tuğrul Tiryaki[1]

[1]*Ankara City Hospital, Clinic of Pediatric Urology, Ankara, Turkey*

[2]*Ankara Training and Research Hospital, Clinic of Pathology, Ankara, Turkey*

[3]*University of Health Sciences Turkey, Gülhane Training and Research Hospital, Clinic of Biochemistry, Ankara, Turkey*

ABSTRACT

Background: Various methods have been investigated to prevent postoperative peritoneal adhesions (PPA). It is thought that wound healing process would be better with the use of platelet rich plasma (PRP).

Materials and Methods: The aim of this study was to investigate the role of PRP in the formation of PPA and in preventing adhesion formation in rats. It was also planned to demonstrate the relationship between serum interleukin (IL)-6 and TNF-alpha levels and the severity of adhesions before creating the adhesion model and during sacrification. Rats were divided into 3 groups, each consisting of twelve rats. Groups were classified as; PRP, sham and control group. The rats were sacrified on the 14th day and relaparotomies were performed.

Results: The results were evaluated macroscopically and microscopically according to predetermined classifications. When the group treated with PRP was compared with the control groups according to the previously described macroscopic (Nair) and microscopic (Zuhlke) classifications, there was no significant difference in PPA formation both microscopically and macroscopically. It is thought that TNF-alpha and IL-6 should be used as markers in PPA formation process.

Conclusion: In the experimentally created adhesion model, the effect of PRP on preventing PPA formation could not be proved.

Keywords: Postoperative peritoneal adhesions, platelet rich plasma, adhesion in rats

ÖZ

Amaç: Ameliyat sonrası peritoneal adezyonları önlemek için çeşitli yöntemler araştırılmıştır. Trombositten zengin plazma (PRP) kullanımı ile yara iyileşme sürecinin daha iyi olacağı düşünülmektedir. Bu çalışmanın amacı, PRP'nin sıçanlarda ameliyat sonrası periton yapışıklıkları (PPA) oluşumunda ve adezyon oluşumunu önlemedeki rolünü araştırmaktır.

Gereç ve Yöntemler: Ratlarda adezyon modeli oluşturulmadan önce ve sakrifikasyon sırasında serum interlökin (IL)-6 ve TNF-alfa seviyeleri ile adezyonların şiddeti arasındaki ilişkinin gösterilmesi planlandı. Sıçanlar her biri on iki rattan oluşan 3 gruba ayrıldı. Gruplar şu şekilde sınıflandırıldı; PRP, sham ve kontrol grubu. Ratlar 14. günde sakrifiye edilerek relaparotomi yapıldı.

Bulgular: Sonuçlar önceden belirlenmiş sınıflandırmalara göre makroskopik ve mikroskobik olarak değerlendirildi. PRP ile tedavi edilen grup, daha önce açıklanan makroskopik (Nair) ve mikroskopik (Zuhlke) sınıflamalara göre kontrol grupları ile karşılaştırıldığında, hem mikroskobik hem de makroskopik olarak PPA oluşumunda anlamlı bir farklılık yoktu. PPA oluşum sürecinde belirteç olarak TNF-alfa ve IL-6'nın kullanılması gerektiği düşünülmektedir.

Sonuç: Deneysel olarak oluşturulan adezyon modelinde PRP'nin PPA oluşumunu önlemedeki etkisi kanıtlanamamıştır.

Anahtar Kelimeler: Postoperatif periton adezyonları, trombositten zengin serum, ratlarda adezyon

Address for Correspondence: Gökhan Demirtaş, Ankara City Hospital, Clinic of Pediatric Urology, Ankara, Turkey
Phone: +90 506 634 02 17 E-mail: drgokhandemirtas@gmail.com **ORCID ID:** orcid.org/0000-0003-0787-2330
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Introduction

Postoperative peritoneal adhesions (PPA) are serious problems after abdominal surgery (1,2,3,4,5). The incidence of small bowel obstruction due to PPA is high in pediatric surgery (6). Among these problems, pain, intestinal obstruction, volvulus and infertility are the most common pathologies (3,7). In the formation of PPA, which is a kind of peritoneal damage; mechanical, ischemic, infective, inflammatory and chemical factors play a role.

Various methods have been searched for the prevention of adhesions and the use of different clinical techniques and medications has come forefront to prevent postoperative adhesion formation. There are two basic processes that can be interfered to minimize PPAs prevention of peritoneal trauma and prevention of adhesion of the damaged peritoneal surface to any surface. The first of these is the prevention of is a much simpler and effective method. By using careful and appropriate surgical technique, ensuring adequate hemostasis, leaving no foreign body or suture material in the abdomen, repairing peritoneal defects without causing tension if possible. The second is careful and appropriate surgical repair of, PPA formation can be prevented by leaving the defect open and fighting against infection by considering that bacteria are among the etiological factors (7). The second stage is a very complex process that begins after the trauma occurs. It is more difficult to tackle the second stage. The pathophysiology of these processes will be relatively low in applications without illumination. Moreover, regardless of the substance and method to be used after trauma; not only it should be non-toxic to peritoneal mesothelial cells, but also it will have to accelerate wound healing or prevent adhesion of mesothelial surfaces until the wound healing process is completed (8). A treatment method that includes all these preventive factors in a substance or method and moreover to optimize. Indeed, no such method has been found to date.

Platelet rich plasma (PRP) is getting popular on medical practice day by day. The platelets perform several essential functions in the body, including blood clot formation and the release of growth factors that help wound healing (9). These growth factors stimulate the stem cells to produce new host tissue as quickly as possible, which is why PRP is so effective in the post-treatment healing process. There have been various studies of PRP used in intra-abdominal procedures. For this purpose, it is planned to investigate the utilization of PRP and how it effects PPA formation.

The aim of this study was to investigate the role of PRP in the formation of PPA and in preventing adhesion formation in rats.

Material and Methods

Before starting the study, an application was made to the Ankara Hospital SAUM Animal Experiments Ethics Committee. Ethics committee approval was obtained at the meeting of the board dated 22.09.2017 by unanimous decision with the decision number 44.

In this study, rats were divided into 3 groups, each consisting of twelve rats. Groups were classified as PRP, sham and control group. In the PRP group, laparotomy was performed, adhesion was created and PRP was applied. In the sham group, laparotomy was performed adhesion was created without PRP. In the control group, laparotomy was performed without adhesion and PRP. The rats were sacrificed on the 14th day and relaparotomies were performed. The results were evaluated macroscopically and microscopically according to predetermined classifications.

Surgical procedures were performed in Ankara Hospital SAUM Experimental Animals Laboratory by providing aseptic conditions. Prophylactic antibiotics were not applied. Intraperitoneal ketamine (Ketalar®, Parke Davis and Co. Inc., 50 mg/kg) and xylazine (Rompun®, Bayer 5 mg/kg) were administered as an anesthetic agent. In order for the rats to be normothermic (37 °C) throughout the study, the temperature of the working environment was maintained with a heating lamp. Glove powder was tried to be removed by washing with sterile saline. After the abdominal skin was shaved and cleaned with 10% poviiodin, laparotomy was performed with a 3 cm midline incision with aseptic surgical technique followed by sterile covering. All subjects received 1 cc of blood from the tail vein before the procedure and were placed in biochemistry tubes. Then, to study the pre-op serum Tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 levels, the blood samples were centrifuged at 4000 rpm for 10 minutes and the serum was separated. Serum samples were placed in Eppendorf tubes (interlab A.C. TR) and stored at -80 °C until analysis day.

Adhesion model: After seeing that there was no adhesion in the abdomen, the cecum was exposed. Then, as a well-defined adhesion model in all rats; after the parietal area corresponding to the cecum was deserosalized, abrasion was formed on the antimezenteric surface of the cecum with a dry gauze. This process was continued until petechial bleeding foci were seen on serosal surfaces.

PRP: Four cc intracardiac blood was taken from each of the eight rats. The bloods were taken into tubes containing gel to separate the erythrocytes, ficoll to separate the white spheres and citrate-dextrose solution as an anticoagulant. The blood samples were delivered to the Ankara Hospital SAUM Biochemistry Laboratory. PRP prepared according to the procedure in the laboratory. After the adhesion model

was created, it was applied as 2 cc to the rats in the PRP group just before the abdomen was closed.

Sacrification and evaluation: In accordance with the Helsinki contract, after the rats were sacrificed with high-dose ether on the 14th day, a maximum view was achieved by making a U incision in the abdomen and retracting the abdominal walls downwards. Adhesions were then evaluated quantitatively with the classification defined by Nair et al. (9) an expression, evaluation was done by two different experts using double blind, in accordance with the criteria given in Table 1. Before sacrification from all subjects, intracardiac 1 cc blood was taken and the blood samples were centrifuged at 4000 rpm for 10 minutes to study the post-operative serum TNF-α and IL-6 levels. Serum samples were placed in Eppendorf tubes (interlab A.C. TR) and stored at -80 °C until analysis day.

In rats that developed adhesion after relaparotomy, the adhesive band was resected together with the affected organs and the parietal peritoneum in those who did not. The pathological specimens were then flicked in containers containing 10% buffered formol. The preparations, which were followed up with the classical laboratory method, were embedded in paraffin blocks. Sections five micrometers thick were taken on the slide. It was stained with hematoxylin-eosin dye and examined by light microscopy. Histopathological and microscopic examination of the samples taken was performed at the Ankara Hospital SAUM Lab of Pathology Department. The pathologist who made the examination did not know from which group the plays were taken. After histopathological evaluation, the preparations were subjected to microscopic grading as defined by Zühlke et al. (10) (Table 2).

Macroscopic Findings

The Nair classification evaluates the severity and extent of adhesion macroscopically. It is classified from 0 to 4 according to the severity and prevalence of adhesions (Table 3).

Tissue samples of approximately 3x2 cm intestinal wall of rats were embedded in paraffin after ethanol dehydration (50%, 75%, 96% and 100% respectively) and xylene translucency after fixation in 10% formaldehyde solution for 2 days. Four microns sections were taken with microtome and examined by staining with hematoxylin-eosin and Mason Trichrome. Histopathological examination was evaluated in OLYMPUS brand, BX51TF model x4, x10, x20, x40 lenses. Changes in the samples of the intestinal wall were evaluated according to the "Zühlke" microscopic adhesion classification with a semi-quantitative scoring system (Table 3).

TNF-α and IL-6 levels: Serum samples taken during the pre-operative period and during sacrification were stored at the SAUM Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Biochemistry Laboratory until the day of analysis in Eppendorf tubes. Serum TNF-α level; SUNRED Rat was detected with TNF-α ELISA kit (unit value pg/mL) (Rat TNF- alpha ELISA Kit, catalog number: 201-11-0765, Shanghai). Serum IL-6 level; detected with SUNRED Rat IL-6 ELISA kit (unit value pg/mL) (Rat IL-6 ELISA Kit, catalog number: 201-11-0136, Shanghai). Serum samples from all groups were studied in the ELISA reader device (UQuant, Biotec instruments, Inc. Vermont, USA) in the Biochemistry Laboratory of the SAUM Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital using Rat TNF-α and Rat IL-6 kits. The results are shown in Table 4 and Table 5.

Table 1. "Nair" macroscopic adhesion classification

Grade 0	No adhesion	No adhesion
Grade 1	Adverse adhesion	One band between organs or between the organ and the abdominal wall
Grade 2	Pronounced adhesion	Two adhesive bands between organs and between the organ and the abdominal wall
Grade 3	Pronounced adhesion	Adhesion of intestinal loops between organs or between the organ and the abdominal wall, with no more than two adhesive band or adhesion to the abdominal wall
Grade 4	Severe adhesion	Viscera adheres directly to the abdominal wall

Table 2. "Zühlke" microscopic adhesion classification

Grade 0	Normal findings
Grade 1	Weak connective tissue, rich cell, old and new fibrin, thin reticulin fibrils
Grade 2	Connective tissue with cells and capillaries, rare collagen fibers
Grade 3	Thicker connective tissue, rare cells, more vessels, rare elastic and smooth muscle fibers
Grade 4	Old thick granulation tissue, poor removal from the cell, difficult separation of serosal layers

Statistical Analysis

While evaluating the findings statistically, IBM SPSS (Statistical Package for the Social Sciences, version 22.0; SPSS Inc., Chicago, IL) program was used in the study. In the analyzes, $p<0.05$ was considered statistically significant (Table 6).

When compared with the groups treated with PRP and the control groups were not significantly different in both microscopic and macroscopic PPA formation compared to the macroscopic (Nair) and microscopic (Zuhlke) previously defined.

Results

When the rats were evaluated according to the macroscopic adhesion classification (Nair's), while no adhesion formation was observed in 8 rats in the PRP group, 1st degree macroscopic adhesion was observed in 2 rats and 3rd degree macroscopic adhesion in 2 rats (Table 3). When the PRP and control groups were compared in terms of macroscopic adhesion, no statistically significant difference was found ($p>0.05$) (Table 6).

When the rats were evaluated according to the microscopic adhesion classification (Zühlke), no adhesion formation was observed in 6 rats, while 1st degree adhesion formation was observed in 2 rats, 2nd degree in 1 rat, 3rd degree in 2 rats and 4th degree in 1 rat (Table 3). When the PRP and control groups were compared in terms of microscopic adhesion, no statistically significant difference was found ($p>0.05$) (Table 6).

The three groups were examined in terms of TNF-α levels, it was found that the postoperative TNF-α levels of the control group were higher than the preoperative levels ($p<0.05$) (Table 4). On the contrary, there was no statistical difference between preoperative and postoperative TNF-α levels of Sham and PRP groups ($p>0.05$). In the statistical evaluation of independent groups in terms of preoperative and postoperative results, there was no difference between the groups' postoperative TNF-α levels, but there was a statistically significant difference between preoperative TNF-α levels ($p<0.05$). While there was no difference between the preoperative TNF-α levels of the control and PRP groups, the preoperative TNF-α levels of the sham

Table 3. Macroscopic and histopathological adhesion rating by groups

Rats	Macroscopic adhesion			Histopathological adhesion		
	PRP	Control	Sham	PRP	Control	Sham
1	0	1	0	0	2	2
2	0	4	4	1	4	4
3	1	0	0	2	1	2
4	3	0	0	3	0	1
5	0	0	0	0	0	1
6	0	1	0	0	1	1
7	0	2	0	0	1	1
8	0	1	0	1	0	1
9	0	1	1	0	1	3
10	0	1	0	0	2	2
11	1	1	1	3	1	4
12	3	1	0	4	1	1

PRP: Platelet rich plasma

Table 4. Pre-op and post-op TNF-α levels in all rat groups

	Control (C)		Sham (S)		PRP (P)		[b]p between groups	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
TNF-α	291±84 322 (60-374)	394±102 382 (258-645)	362±30 358 (294-402)	407±82 389 (307-569)	314±42 317 (220-369)	334±148 276 (179-622)	0.0030	0.0924
[a]p	0.0002		0.1506		0.4548			
					***Pre-op**		<0.01, >0.05, <0.05	

group were higher than the preoperative TNF-α levels of the control and PRP groups (p<0.05).

The groups were analyzed in terms of IL-6 levels, it was found that the postoperative IL-6 levels of the control and sham groups were higher than the preop levels, unlike the PRP group (p<0.05) (Table 5). There was no statistical difference between the preoperative IL-6 levels of all three groups (p>0.05). Similarly, there was no statistical difference between the postoperative IL-6 levels of all three groups (p>0.05) (Table 5).

Discussion

PPAs is one of the major complications of abdominal surgery in children (1,2,3,4,5). The incidence of postoperative small bowel obstruction in children ranges from 2% to 30% and the incidence was 57% greater in neonates than in infants and children. Of all types of abdominal surgery, open colorectal surgery was found to result in the highest rate of adhesion-related readmissions (10,11). Unfortunately, there are not any devices able to totally prevent the intraperitoneal adhesion formation after abdominal surgery; only the use of correct surgical technique and the avoidance of traumatic intraperitoneal organ maneuvers may help to reduce postoperative adhesion incidence.

PPAs following abdominal surgery are among the most important causes of long-term morbidity. Therefore, studies on preventing PPAs are increasing day by day in the literature. PPAs can cause recurrent pain, intestinal obstructions, volvulus and infertility. For these reasons, patients need recurrent, outpatient or inpatient treatment, some patients even have to undergo surgery. In addition to the additional morbidity that this situation brings to patients, it is also reflected as a serious burden on health expenditures. A method that prevents the formation of PPA will eliminate repetitive surgeries and its morbidity and financial burden (12,13). In order to prevent PPA formation, it has been tried in many mechanical and physiological methods (14,15).

Platelet concentrates for topical and infiltrative use are used or tested as surgical adjuvants or regenerative medicine preparations in most of the medical fields, particularly in sports medicine and orthopedic surgery. These preparations are used on the surgical or wounded site in order to stimulate, improve and accelerate healing (12). Platelet-derived factors have been extensively used for clinical and surgical applications requiring tissue regeneration.

PRP has also been used in intra-abdominal operations. Since the positive effects of PRP on colon anastomosis has been shown in most of these studies and PRP has become a popular natural concentrate for wound healing

Table 5. Pre-op and post-op IL-6 levels in all rat groups

	Control (C)		Sham (S)		PRP (P)		[b]p between groups*	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
IL-6	29±8 29 (19-41)	58±34 42 (24-123)	34±7 36 (22-45)	52±22 45 (22-92)	31±3 32 (28-37)	42±22 32 (20-82)	0.2019	0.2053
[a]p	0.0012		0.0034		0.3110			

[a]Wilcoxon matched-paired test, [b]Kruskal-Wallis test (non-parametric ANOVA): The p-value is approximate (from chi-square distribution). * If p-value obtained by ANOVA is <0.05, p-values of between groups (respectively, C and S, C and P, and S and P) are compared with post-test and non-parametric data are given as mean, standard deviation and median (minimum-maximum). IL-6: Interleukin-6, PRP: Platelet rich plasma

Table 6. Comparison of control and PRP groups in terms of macroscopic and microscopic adhesion

		Control group n=12 (%)	PRP group n=12 (%)	p
Nair	Normal	9 (75)	8 (66.7)	0.383
	Oneband	2 (16.7)	2 (16.7)	
	Multiplebands	0	0	
	Organ adhesion	0	2 (16.7)	
	Dens ad	1 (8.3)	0	
Zuhlke	Normal	0	6 (50)	0.174
	Simple	6 (50)	2 (16.7)	
	Complex	3 (25)	1 (8.3)	
	Serious	1 (8.3)	2 (16.7)	
	Severe	2 (16.7)	1 (8.3)	

PRP: Platelet rich plasma

and anastomotic healing. Therefore, this study was planned to evaluate whether or not PRP prevents intra-abdominal adhesions.

PRP, is the name given to plasma in high platelet concentrations. There is no clear definition for this limit value, the average increase is considered to be "4-5 times" (14,16). PRP was first used by M. Ferrari (in 1987) as an autologous blood product transfusion component after open heart surgery. By using PRP, it is aimed to transfer biological molecules to the highest level of damaged tissue, which increases tissue regeneration in platelets. Due to its natural and reliable use, its popularity is increasing day by day. With recent studies, growth factors and cytokines in platelets include; it has been shown to be highly effective in inflammation, postoperative blood loss, infection and wound healing. In addition, platelets secrete bioactive proteins involved in macrophage and mesenchymal stem cell activation. Thus; not only they clean damaged and necrotic tissues, they also contribute to tissue regeneration and healing positively (17).

Alpha granules in platelets acts as a depot for growth factors in inactive state and cell growth, differentiation, cytokine release, angiogenesis; they show anti-apoptotic effect by stimulating collagen synthesis and chemotaxis. Complex interaction between growth factors and adhesion proteins such as fibronectin and vitronectin manage the regenerative process with chemotaxis, cell proliferation, tissue debris removal, angiogenesis and provides wound healing (18). In order to demonstrate the effect of PRP on PPA, PRP was applied to a group. As a result of the analysis, when the PRP group and the control group were compared, no statistical difference was observed.

Lymphocytes and macrophages; during mesothelial damage repair, they play an important role in the synthesis of growth factors that control fibroblast proliferation and collagen formation. Cytokines such as "platelet-derived growth factor", TGF-β, "fibroblast growth factor", IL-1, IL-6 and TNF-α can be counted among these. Peritoneal damage and microorganisms have been found to activate a large number of inflammatory mediators along with "early response cytokines" such as tumor TNF-α, IL-1, IL-6 by triggering cellular defense mechanisms of the host organism such as endotoxin. Future treatment strategies should aim to control cellular mediators in the peritoneal fluid at the beginning of the adhesion formation process (19). These mediators include IL-1α, TGF-α, EGF, TGF-β, IL-6 and TNF-α. In our study; in order to demonstrate the effect of PPA and cytokine levels, TNF-α and IL-6 results from samples taken before the procedure and before sacrification were examined. In subjects with high PPA formation; TNF-α and IL-6 levels were observed to be high. In the literature; there are studies supporting IL-10 to be adhesion preventive (20). TNF-α and IL-6 are thought to be used as markers in the PPA formation process.

Conclusion

In the experimentally generated adhesion model, the effect of PRP on preventing PPA formation could not be proved. TNF-α and IL-6 might be used as PPA formation markers.

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Ethics

Ethics Committee Approval: The study, an application was made to the Ankara Hospital SAUM Animal Experiments Ethics Committee. Ethics committee approval was obtained at the meeting of the board dated 22.09.2017 by unanimous decision with the decision number 44.

Informed Consent: Ethics committee approval was obtained as it was an animal experiment and it has been studied in accordance with the Helsinki Declaration.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.D., H.T.T., Concept: G.D., Design: H.T.T., Data Collection or Processing: G.D., M.K., S.H., Analysis or Interpretation: G.D., P.C., Literature Search: G.D., H.T.T., Writing: G.D.

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An Economic Evaluation of Generic Drug Entries in Turkish Pharmaceutical Market

Türkiye İlaç Pazarında Jenerik İlaç Girişlerinin Ekonomik Olarak Değerlendirmesi

Güven Bektemür[1], Esra Şafak Yılmaz[2], Enver Kağan Atıkeler[3], İsmail Mert Vural[4], Seray Nacar[3], Aslıhan Beyan[3], Banu Bayar[3], Hakkı Gürsöz[3]

[1]*University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Department of Health Management, Istanbul, Turkey*

[2]*University of Health Sciences Turkey, Gülhane Faculty of Medicine, Department of Medical Informatic, Ankara, Turkey*

[3]*Turkish Medicine and Medical Devices Agency, Ankara, Turkey*

[4]*University of Health Sciences Turkey, Gülhane Faculty of Pharmacy, Ankara, Turkey*

ABSTRACT

Background: The widespread use of generic medicines in Turkey will reduce pressure on the budgetary burden resulting from new treatments and facilitate access for more patients. Therefore, it is important to analyze the effects of the new generic drugs on the equivalent market in Turkey. The objective of the paper is to study the effects of generic entry on the price of the original drug and show the generic competition with increased number of generic drugs in Turkish Pharmaceutical Market.

Materials and Methods: We evaluated 46 equivalent groups and 256 medicines. We assessed the groups that generic equivalents of original products market entry after January 2007 for ten years period in Turkey. Unit prices (TL) were calculated with using monthly sales (TL) and monthly unit sales quantities obtained from Quintiles and Intercontinental Marketing Statistics database. In order to calculate the generic market entry effect in each generic equivalent group, we calculated the 12-month average unit price of original drug before first generic entry and we calculated the 12-month average unit price of original drug after the first generic entry.

Results: We observed that in this study, 39 original products average prices decrease was 25.85% [standard deviation (SD±10.2%) and 10 products average price increase was 5.59% (SD±6.3) when a generic medicine first appeared in the market. On the evaluated equivalent groups, the original drug prices were significantly decreased when the generic drugs entered to the market.

Conclusion: This paper concerns the impact of generic competition on the market unit price ratio of original drugs and has shown that the effects of new generic entrance to market on original drug unit price are significant and enduring. But this effect ends with the entry of 6th generic drug. Therefore, if there are more than 6 generics there will be no more price drops.

Keywords: Generic drug competition, generic drug entry, Turkish pharmaceutical market

ÖZ

Amaç: Türkiye'de jenerik ilaçların yaygınlaşması, yeni tedavilerin bütçe üzerindeki baskısını azaltacak ve daha fazla hastanın erişimini kolaylaştıracaktır. Bu nedenle, yeni jenerik ilaçların Türkiye'deki eş değer pazar üzerindeki etkilerinin analiz edilmesi önemlidir. Bu çalışmanın amacı, jenerik girişinin orijinal ilacın fiyatı üzerindeki etkilerini incelemek ve Türkiye İlaç Pazarı'nda artan jenerik ilaç sayısı ile jenerik rekabetini göstermektir.

Gereç ve Yöntemler: Kırk altı eş değer grubu ve 256 ilaç değerlendirildi. Türkiye'de Ocak 2007'den sonra orijinal ürünlerin jenerik eş değerlerinin pazara giriş yaptığı gruplar on yıllık dönem için değerlendirildi. Birim fiyatlar (TL), IQVIA veri tabanından elde edilen aylık satış (TL) ve aylık birim satış miktarları kullanılarak hesaplanmıştır. Her bir jenerik eş değer grupta jenerik pazara giriş etkisini hesaplamak için ilk jenerik girişten önce orijinal ilacın 12 aylık ortalama birim fiyatını ve ilk jenerik girişten sonra orijinal ilacın 12 aylık ortalama birim fiyatı hesaplandı.

Bulgular: Bu çalışmada, bir jenerik ilacın piyasa içinde ilk ortaya çıktığında 39 orijinal üründe ortalama fiyat düşüşünün %25,85 [standart sapma (SS)±10,2 ve 10 üründe ortalama fiyat artışının %5,59 (SS±6,3) olduğunu gözlemledik. Değerlendirilen eş değer gruplarda, jenerik ilaçların piyasaya girmesiyle orijinal ilaç fiyatları önemli ölçüde düşmüştür.

Address for Correspondence: Güven Bektemür, University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Department of Health Management, Istanbul, Turkey
Phone: +90 546 578 28 28 E-mail: guvenbek@gmail.com **ORCID ID:** orcid.org/0000-0001-5899-566X

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ÖZ

Sonuç: Bu makale, jenerik rekabetinin orijinal ilaçların piyasa birim fiyat oranı üzerindeki etkisiyle ilgilidir ve piyasaya yeni jenerik girişin orijinal ilaç birim fiyatı üzerindeki etkilerinin önemli ve kalıcı olduğunu göstermiştir. Ancak 6. jenerik ilacın girişi ile bu etki sona erer. Bu nedenle, 6'dan fazla jenerik varlığında daha fazla fiyat düşüşü olmayacaktır.

Anahtar Kelimeler: Jenerik ilaç rekabeti, jenerik ilaç girişi, Türkiye ilaç pazarı

Introduction

Turkey is one of the developing countries considering size of pharmaceutical industry. Turkish pharmaceutical market reached to double size on value basis from 2008 to 2017. This increase is proportional to the world pharmaceutical market. According to the Pharmaceutical Manufacturers Association of Turkey data, Turkish pharmaceutical market was TL 13.4 billion in 2010 and this number increased to TL 30.9 billion in 2018 (1). With the Health Transformation Program initiated in 2003 and the Social Security Reform carried out in 2006, there have been many developments affecting the pharmaceutical market and facilitating access to drugs.

In Turkey, pharmaceutical access to the market after obtaining registration granted by the Turkish Medicine and Medical Devices Agency (TMMDA).

In Turkey, drugs are allowed to enter the market after obtaining the license issued by the TMMDA.

Generic or original, all new drug prices are determined by TMMDA at the end of the marketing authorization process. An originator product can be priced up to 100% of the reference price until its first generic enters the market. Once a generic is introduced to the market both the originators and the generics are priced at 60% of the reference price.

Companies apply to social security institution (SSI) for reimbursement in order to enter the positive reimbursement list after marketing authorization is granted and retail price is set. Reimbursement decision is the responsibility of the inter-ministerial reimbursement commission (RC). For all pharmaceuticals, companies have to apply to the Medical and Economic Appraisal Committee (MEAC) with a reimbursement dossier which contains general information of the product, clinical data and literature review with pharmacoeconomic evaluation of the product. MEAC assesses all dossiers and declares its decision to RC which is responsible from the reimbursement decision and then RC finalizes the decision.

Due to the interventions developed for the increasing domestic production capacity in Turkey, analysis and evaluation of generic market were needed. The changes in the reimbursement policies made by the SSI (Alternative Reimbursement Applications, Localization Policies, etc.) have also been adopted by Ministry of Health and other related stakeholders in over years. As in other European countries, the widespread use of generic medicines in Turkey and its encouraging will reduce pressure on the increased budgetary burden due to new treatments on public finance and facilitate easier access for more patients with the same budget. Therefore, it is important to analyze the effects of the new generic access on the equivalent market in Turkey.

The objective of the paper is to study the effects of generic entry on the price of the original drug and show the generic competition occur on the conditions of increased generic drug number situation.

Material and Methods

In the study, monthly data were used from Quintiles and Intercontinental Marketing Statistics (IQVIA) between the years 2007-2017, which was renamed IQVIA in 2017 and formerly known as QuintilesIMS (Quintiles and IMS).

An equivalent group is a group of drugs whose active substance(s), pharmaceutical forms and unit amounts of raw material are the same form. The list of equivalent groups, which are in the positive list was updated and published by SSI. In this study, 1.523 equivalent groups and 5.458 drug forms published by SSI and updated by IQVIA in August 2017 were evaluated. Some criteria were used to evaluate the generic entry into the market. The generic equivalent groups of the original products that entered the market in Turkey after January 2007 were evaluated. Due to database restriction, the previous period (monthly) of January 2007 could not be evaluated. Molecules in these groups will be referred to as original or generic depending on which product first entered the market. For this reason, equivalent groups with the original drug were selected as the first drug to enter the equivalent group. Those containing more than one original drug in the same group and equivalent groups containing only one drug in the equivalent group were also excluded from the study. Thus, 46 equivalent groups and 256 drugs were evaluated according to these criteria.

Unit prices were obtained by the ratio of IQVIA monthly sales (TL) to monthly box sales quantities. In order to calculate the generic entrance effect in an equivalent group, the 12-month average unit price of the original drug before the introduction of the first generic drug and the 12-month average unit price of the original drug after the introduction

of the first generic drug were calculated. The price change rate was calculated based on the price of the original product. This calculation continued for second, third, fourth and fifth generic entrance.

Ethics committee approval is not required for the study.

Statistical Analysis

The effect of the initial number of generic competitors was analyzed using analysis of variance (ANOVA) and post-hoc analysis was performed. Linear-by-Linear Association analysis was used to assess the relation between market life and price ratio of the original drug. Comparisons between original drug prices were made with using Student's t-test. Statistical analysis was made using IBM SPSS Version 22.0 and p-values of <0.05 were considered statistically significant.

Results

In Turkey, generic drug ratio is always more than the original drugs regarding unit sales. Beside this, generic drugs market share was only 30-35% of drug expenditure between 2011-2016 (Table 1).

We have 1.523 equivalent groups and 5.458 medicines. One thousand four hundred eighty-three of these are original medicine and 3.975 are generic. Nine-hundred sixty-one equivalent groups have original product as first drug in the group. Groups have 3.8 drug in average. Figure 1 shows distribution of the first generics of these groups by year of entrance. After an average of 8.89 years, there was an original drug entry into the generic competitive market.

The prices ratio of the 39 original products average prices decrease was 25.85% (SD±10.2%) and 10 products average price increase was 5.59% (SD±6.3) when a generic medicine first appeared in the market. On the evaluated equivalent groups, the original drug prices were significantly decreased when the generic drugs entered to the market. Figure 2 shows the price ratio for original drugs when they first started generic competition as a function of the number of generic competitors. Having one or more generics was associated with additional decline in the price of the original drugs. This decline is statistically significantly decreasing as the number of generics increases (p<0.001). As we noticed with post-hoc analysis of ANOVA having six or more generics was associated with a decline in the price of the original drugs compared to the situation where there was a single case (p<0.001). The effect of the first generic entry was seen at 19.6%, but when the generic number increased to 6 or more, the fall in the original price was 3.8%.

Table 2 shows unit price ratios of original drug after generic entry according to market age of original drug. As for the correlation analysis, there is no statistical relationship between unit price ratios of the original drug after first generic entry according to market age of original drug (p=0.872). Additionally, this situation is the same as other generic number.

Table 1. Annually market share of generic drug

	Generic drug ratio (unit)	Generic drug ratio (TL)
2011	52.9%	36.4%
2012	53.1%	36.0%
2013	53.6%	35.3%
2014	54.3%	29.4%
2015	55.1%	29.5%
2016	56.6%	30.7%

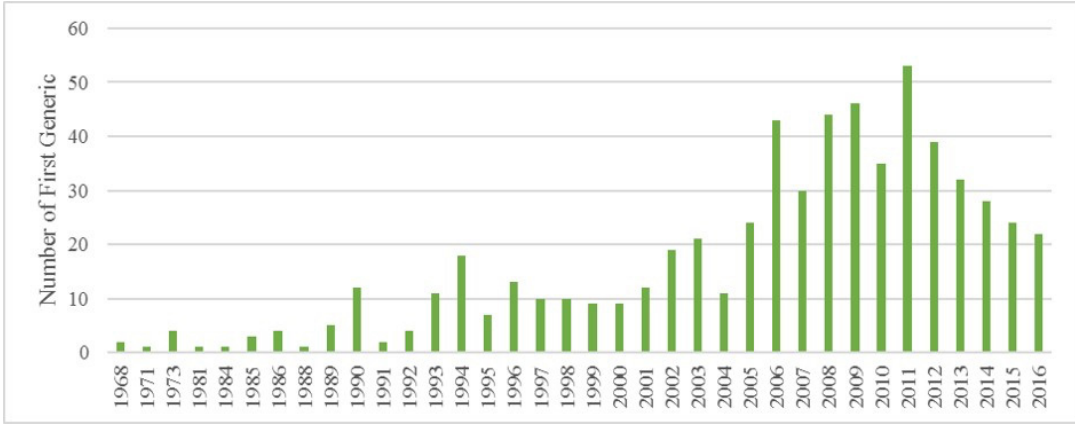

Figure 1. Annual first generic entrance, an equivalent group

Discussion

Physicians and pharmacists can persuade patients for the pharmacological equivalence of drugs and all drugs can switch between equivalent groups. There is a real switching cost between drugs. However, if a better product or a lower price is offered, price switching costs can be overcome. Although original products and generics have the same chemical substance, some consumers may have the impression that the brand-name product is better, so we do not assume homogeneity among the products, not because of their nature, but because of the perception of some consumers which is a consequence of brand loyalty (2,3).

Table 2. Unit price ratios of original drug after first generic entry according to market age of original drug

Market age of the drug (year)	Unit price ratios of original drug
2	-20.3%
3	-36.7%
4	-9.1%
5	7.7%
6	-11.6%
7	19.8%
8	-18.8%
9	-22.6%
10	-31.2%
11	-17.3%
	p=0.872

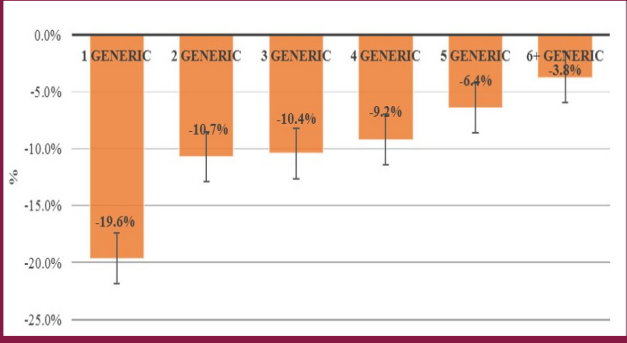

Figure 2. Effect of number of generic competitors on price of original product at time of introduction of generic competition. Unit price ratio of original products (one-year average unit price in when generic competition starts/one year average unit price in edition preceding introduction of generic competition; unit price is division of monthly unit sales to cost). Analysis of variance. *p<0,001 compared to six or more generics. Bars represent 95% confidence intervals

In Turkey, generic drug ratio is always more than the original drugs regarding unit sales. Beside this, generic drugs market share was only 30-35% of drug expenditure between 2011-2016. This paper concerns the impact of generic competition on the market unit price ratio of original drugs and our study has shown that the effects of generic drug entrance to market on original drug unit price are significant and enduring. According to study result, first decline of original drug price was due to the price policy in Turkey, the most important parameter affecting price change is the competition between products in the following years. But this effect ends up with more than 6 generic entries. While the data in this study is restricted to last 10 years, it is likely that being first generic into the market has more effects on original drug market share.

The lack of price competition may lead to increased costs in the market. When generics first became available having one generic was associated with a decrease in the price of the original drugs and compared to having two, three, four, five or six and more generic competitor, first generic has the highest effect.

There are lots of studies to explain the generic competition in literature. Frank and Salkever (2) looked at a sample of 32 drugs that lost patent protection. More competition among generic drug producers is found to cause price reductions for those drugs. Increased competition from generic drugs, however, is not accompanied by lower prices on branded drugs. Instead, their results suggest a small price increase on branded drugs.

In the study of Caves et al. (4) they investigate 30 drugs that lost patent protection between 1976 and 1987. The branded drug price declines with the number of generics. For the mean number of generic drugs, the original drug price declines by 4.5% only. At the same time generic prices are much lower than the brand name prices. This study has shown that average generic price is about 50% of the original drug price when three generic producers have entered the market.

Some of studies about generic competition have shown that the market share of the originator drug falls after patent expiry, but a small market share remains, despite the relatively higher price compared to generics (5,6,7).

In another study, it was shown that the generic effect of the brand loyalty is not prevented. The prices of generic drugs are lower than the prices of original drugs after the end of patent (3). Also Kanavos et al. (5) has shown that in the United States the average difference between original drug price and generic price up to 3 years after first entry is 80% and that the average generic drug entrance up to 3 years after first entry is 55%; in Germany, the original drug

price would have to decrease by 25-40% in order to regain a maximum of 45% of the market (7).

Brekke et al. (8) argue that the reference price application in original and generic competition is more effective than price ceilings.

Mats and Niklas (9) found that generic entry in Sweden led to a significant decrease in drug prices with the reference price system.

Grabowski et al. (10) found that generic medicines provide financial benefits to patients and reimbursement institutions in the United States. They came to the conclusion that generic competition caused significant price reductions in original drugs.

Aronsson and his colleagues showed that generic drug entry reduces market share of original drugs due to price competition and affects their prices (11).

Saha et al. (12) found that generic drug competition had a significant impact on important drugs with a high market share, especially called blockbuster, and the market share decreases resulted with lower prices of original drugs. It has been determined that this decrease in price is directly proportional to the increase in the number of generics.

Danzon et al. (13) have found that generics have reached a high market volume in the first year in the market, which is more likely the result of patients' interest and pharmacists' generic substitution.

Espin and Rovira (14) mentioned in the reports funded by the European Commission; it is easier to integrate use of generics with countries with single reimbursement agencies. According to the data obtained from the study, it has been proven in Sweden that generics saved around 760 million Euros between October 2002 and December 2005.

Mossialos et al. (15) reported that the introduction of ceiling prices for therapeutic groups in the United Kingdom with generic entry has resulted in savings of 474 million euros (2002) by reducing reimbursement prices. Puig-Junoy (16) done the literature review covering the years 2000 to 2009, it was determined that generic entry and competition in countries with ceiling price implementation were inadequate to lower prices, but prices of all drugs fell in groups with generic competition in countries with a reference price system. Wouters et al. (17) compared generic medicine markets and they found out that different generic incentives could affect use of generics such as pricing, prescribing, and substitution policies. Based on the studies price competition has direct effect on physicians' prescription and pharmacist dispense which resulted with increased generic use and cost-saving for payer.

Countries has policies to increase generic uptake. There are two important tools following; generic substitution and prescribing by International Non-proprietary Name (INN). In a report published by World Health Organization, 45 countries were examined and in that 41 countries allowed generic substitution while it is obligatory in 14 of those countries. In the study it is examined that INN prescribing has been implemented in many countries and allowed in 24 countries and obligatory in 17 countries. Many countries clustered medicines into reference group based on therapeutic area and use internal reference pricing for reference groups. Patients has to pay difference in case if they wish to use expensive medicine in the reference group. The reference pricing system is financial incentive for patients to use generics in order to avoid co-payments.

Northern European Countries reduced prices with generic availability with tendering, results seem much more effective than more regulated generic policies not just for pricing also for generic uptake (18). But this policy may also result in high price differences between originator and generic in some therapeutic groups (19).

Twenty-five European countries support generic use by using INN prescribing and it is mandatory in 10 of them (20). Tenders and INN prescription system increase generic uptake and allow price competition between originator and generics. As mentioned in the article written by Kaplan et al. (21) government policies for pharmaceutical market that allow early entry to market for generics together with or without financial incentives for use of generics can achieve both increasing generic consumption and price competition.

Conclusion

This study concerns the impact of generic competition on the market unit price ratio of original drugs and has shown that the effects of new generic entrance to market on original drug unit price are significant and enduring. But this effect ends with the entry of 6th generic drug. Therefore, if there are more than 6 generics there will be no more price drops. While the data in this study is restricted to last 10 years, it is likely that being the first generic product to enter the market, has more effects on original drug market share.

Ethics

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

Informed Consent: Not necessary.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.B., E.Ş.Y., Design: E.K.A., İ.M.V., H.G., Data Collection or Processing: E.Ş.Y., S.N., B.B., Analysis or Interpretation: H.G., İ.M.V., Literature Search: G.B., E.K.A., B.B., Writing: G.B., E.Ş.Y., A.B.

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The Effect of Different Anesthesia Techniques on Strabismus Surgery: A Prospective Observational Study

Farklı Anestezi Tekniklerinin Şaşılık Cerrahisi Üzerine Etkisi: Prospektif Gözlemsel Çalışma

Bülent Barış Güven[1], Mehmet Mutlu[2], Seray Türkmen[2]

[1]*University of Health Sciences Turkey Hamidiye Faculty of Medicine; İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey*

ABSTRACT

Background: Strabismus correction surgery is the most common eye operation in children. This present study aims to evaluate the effects of orotracheal intubation using a neuromuscular blocking agent (NMA) in strabismus surgery anesthesia and laryngeal mask airway (LMA) application using total intravenous anesthesia without using NMA on the deviation angles measured following strabismus surgery.

Materials and Methods: ASA I-II group patients with concomitant horizontal strabismus, aged under 14, scheduled for strabismus surgery under general anesthesia were prospectively examined for the study. The study did not include those with restrictive type strabismus, vertical deviation, intraoperative vertical muscle group treatments, anisometropia, and corrected visual acuity less than 0.8. According to the order of arrival, either OTE was conducted with NMA, or LMA (LMA-group) was used without NMA for general anesthesia in patients.

Results: The study included 49 patients, divided into LMA (n=24) and OTE (n=25). The patients' mean age was 8.04±3.63 years. The distribution was similar between groups, with 63% (n=31) having esotropia and 37% (n=18) having exotropia. Angles of deviation were measured to be above 10 prism diopter in 1 patient in the LMA group and two patients in the OTE group at the end of postoperative 1st month. There was no statistically significant difference between the groups regarding decreased postoperative deviation angles and preoperative-postoperative deviation angle measurements.

Conclusion: The tone changes in the eye muscles using NMAs in strabismus surgery anesthesia caused no changes in the postoperative deviation angles or the surgical result.

Keywords: Anesthesia, surgery, strabismus

ÖZ

Amaç: Strabismus düzeltme operasyonları çocuklarda en sık yapılan göz operasyonlarındandır. Bu çalışmada amacımız şaşılık cerrahisi anestezisinde nöromusküler blokör ajan (NMA) kullanılarak yapılan oratrakeal entübasyon (OTE) uygulaması ile NMA kullanılmadan total intravenöz anestezi kullanılarak yapılan laringeal maske airway (LMA) uygulamasının şaşılık cerrahisi sonrası ölçülen kayma açılarına etkisini değerlendirmektir.

Gereç ve Yöntemler: Genel anestezi altında şaşılık cerrahisi planlanan concomitant horizontal yönde şaşılığı bulunan, ASA I-II grubu, 14 yaş altındaki hastalar çalışma için prospektif olarak değerlendirmeye alındı. Restriktif tip strabismusu olanlar, vertikal yönde kayması olanlar veya intraoperatif vertikal kas gruplarına da müdahale edilenler, anizometropisi bulunanlar ve düzeltilmiş görme keskinliği 0,8'in altında olanlar çalışma dışı bırakıldı. Hastalara genel anestezi için geliş sırasına göre ya NMA uygulanarak OTE yapıldı ya da NMA uygulanmadan LMA (LMA-group) kullanıldı.

Bulgular: LMA-grubu (n=24) ve OTE-grubu (n=25) olmak üzere toplam 49 hasta çalışmaya alındı. Hastaların yaş ortalaması 8,04±3,63 yıl idi. Hastalıkların %63'ünde (n=31) esotropia varken, %37'sinde (n=18) eksotropia vardı ve gruplar arasındaki dağılımı benzerdi. Postoperatif birinci ayın sonundaki kayma açısı LMA-grubunda 1 hastada, OTE-grubunda ise 2 hastada 10 prizma diyoptri üstünde

Address for Correspondence: Bülent Barış Güven, University of Health Sciences Turkey Hamidiye Faculty of Medicine; İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Phone: +90 533 638 34 45 E-mail: barguv@gmail.com **ORCID ID:** orcid.org/0000-0002-3628-7408

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ÖZ

ölçüldü. Preoperatif ve postoperatif kayma açıları ile postoperatif kayma açısı ölçümlerindeki azalma açısından gruplar arasında istatistiksel olarak anlamlı bir fark gözlenmedi.

Sonuç: Şaşılık cerrahisi anestezisinde NMA'ların kullanılması ile göz kaslarında oluşan tonus değişikliği postoperatif kayma açılarını etkilememiş ve cerrahi sonucu değiştirmemiştir.

Anahtar Kelimeler: Anestezi, cerrahi, şaşılık

Introduction

Children with strabismus account for 3-5% of all children, with correction surgeries the most prevalent among eye operations (1). Most pediatric ophthalmic procedures are done under general anesthesia (2). Under general anesthesia, airway patency is maintained through endotracheal intubation or the use of a laryngeal mask airway (LMA). LMA is a more practical and less invasive procedure in the current anesthetic practices preferred over endotracheal intubation, especially in short-term surgeries and patients with difficult airways in emergencies. The LMA's design maintains epiglottis patency, allowing for easier ventilation. Air leakage is avoided using the inflatable cuff. The main benefit is that there is no requirement for muscle relaxation, and there are fewer postoperative respiratory problems than orotracheal intubation (OTE) (3,4).

In strabismus surgery, the extraocular muscles are millimetrically shortened or lengthened to treat the impairment. Different anesthetic procedures may produce varying degrees of muscle tone loss during the application of anesthesia, resulting in inaccurate surgical correction results. The systemic effects of various anesthetic procedures in strabismus surgery have been mainly studied in patients in the literature so far (1,2,4). However, there is limited research on the outcomes of anesthetic procedures in strabismus surgery (5,6). The present study aims to evaluate the effects of OTE using a neuromuscular blocking agent (NMA) in general anesthesia and LMA application using total intravenous anesthesia (TIVA) without using NMA on the deviation angles measured following strabismus surgery.

Material and Methods

This study was designed as a single-center prospective observational study. Ethics committee approval was obtained at the Clinical Research Ethics Committee of Okmeydanı Training and Research Hospital meeting, dated 07/08/2018, with the decision numbered 48670771-514.10.

The study was carried out with patients who had strabismus surgery under general anesthesia in Okmeydanı Training and Research Hospital Kasımpaşa Additional Service Building between September 2018 and September 2019. SA I-II group patients aged under 14, who were scheduled for surgery under general anesthesia and had deviation angles of 15 prism diopter (ΔD) and above due to strabismus, as well as non-paralytic horizontal strabismus, were assessed in the study. In cooperative patients, the visual acuity was assessed using the Snellen chart and form optotypes, while in non-cooperative patients, it was inferentially determined according to the fixation quality. After securing cycloplegia, a refraction was examined using a retinoscope and auto refractometer. Anterior and posterior segments were evaluated using slit-lamp and ophthalmoscope. The fixation and object tracking features were examined in non-cooperative cases, while the Worth 4-point test was employed to identify the eye to be operated on. Globe movements were assessed in nine cardinal gaze positions, and instances were classified as esotropia or exotropia. In cooperative cases, deviation angles were evaluated using the prism cover test, while in non-cooperative cases, they were assessed using the Krinsky or Hirschberg test. Those with lens, cornea, retina, or optic nerve pathologies that may cause visual impairment, those with restrictive type strabismus, those with vertical shifts or those who had intraoperative vertical muscle interventions, those with mental retardation, those with over 2 ΔD refractive deficiency (anisometropia) between both eyes or in one eye, those with corrected visual acuity less than 0.8, those who were re-operated for strabismus and those who refuse to participate in the study were excluded.

The patient's parents were informed about the study, and their written consent was obtained. None of the patients were given pre-medication. General anesthesia was induced with intravenous propofol (2-3 mg/kg) and maintained with sevoflurane. Consecutively, either OTE (OTE-group) was applied to patients using rocuronium under maintenance anesthesia with sevoflurane (1-2 minimal alveolar concentration), and remifentanil (0.1-0.4 µg/kg/min), or LMA (LMA-group) was applied under TIVA using propofol (6-9 mg/kg/hour) and remifentanil (0.1-0.4 µg/kg/min). Horizontal (lateral and medial rectus) muscle resections with or without recession were performed in all the

cases. In all cases, it is intended for post-surgery deviation angles to be ten ΔD and below. All these procedures were performed by the same specialist using the same methods. Side effects were recorded, including postoperative nausea and vomiting (PONV) and oculocardiac reflex (OCR). OCR was defined as a reduction of at least 15% in baseline heart rate or dysrhythmia. Those with a heart rate of less than <65 beats/min (bradycardia) were given 0.02 mg/kg atropine intravenously. Those experiencing complications of nausea and vomiting within the 2nd post-operative period were identified as PONV, and they were treated with intravenous 0.1 mg/kg ondansetron. Patients were routinely called for an examination on the post-operative 1st day, 1st week, and the 1st month. A physician who was not involved in the study kept track of the patients' postoperative complications and deviation angles at the end of the first month. Demographic data, anesthetic duration, complications, and preoperative and postoperative deviation angles of patients in both groups were compared statistically.

Statistical Analysis

Number Cruncher Statistical System software was used for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the data. The conformity of quantitative data with the normal distribution was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests and visual examinations. The student t-test was used for the binary intergroup comparisons of the quantitative data with a normal distribution. In contrast, the Mann-Whitney U test was used for the binary inter-group comparisons of the quantitative data without normal distribution. The Pearson chi-square test was used to compare the qualitative data. The Wilcoxon Signed Ranks test was used for non-normally distributed parameters intergroup comparisons. The significance was evaluated as minimum $p<0.05$.

Results

Eighty-nine pediatric patients diagnosed with strabismus were assessed during the study. Out of 36 patients who did not meet the study's criteria, 12 had anisometropia, 9 had inadequate visual acuity, 12 had vertical strabismus, and 3 had restrictive strabismus. Fifty-three patients were consecutively divided into the LMA group (n=26) or OTE (n=27). One patient in the LMA group and two patients in the OTE group were eliminated from the study because at least one of the intraoperative vertical muscle groups was intervened. One patient in the LMA group failed to show up for the postoperative follow-up. As a result, 24 patients in the LMA group and 25 patients in the OTE group had their data analyzed (Figure 1).

Of the cases included in the study, 33% (n=16) were female and 67% (n=33) were male. The participants' ages ranged from 2 to 14, with a mean of 8.04±3.63 years. Body mass index (BMI) measurements ranged from 20.6 to 25.8 kg/m^2 with a mean value 22.20±1.25 kg/m^2 There was no statistical difference between the LMA and OTE groups in terms of gender (p=0.232), age (p=0.469) and BMI levels (p=0.109) (Table 1).

While esotropia was found in 63% (n=31) of the cases, exotropia was found in 37% (n=18), and there was no statistical difference in the distribution between the two groups (p=0.769). In the study, the mean duration of anesthesia was 49.5±9,9 minutes, with 7.6±12.1 minutes in the LMA group and 51.1±8.2 minutes in the OTE group. Bradycardia OCR was noted in 16 patients throughout the intraoperative phase, and 10 cases were treated with intravenous atropine, whereas bradycardia resolved

Table 1. Demographic and preoperative clinical data of the patients

		Total (n=49)	LMA-group (n=24)	OTE-group (n=25)	p
Age (year)	Mean ± SD	8.04±3.63	7.78±3.74	8.30±3.55	**0.469**
Gender; n (%)	Female	16 (33)	10 (42)	6 (24)	**0.232**
	Male	33 (67)	14 (58)	19 (76)	
BMI (kg/m^2)	Mean ± SD	22.20±1.25	22.00±1.05	22.40±1.40	**0.109**
Anesthesia time (min)	Mean ± SD	49.5±9.9	47.6±12.1	51.1±8.2	**0.456**
PONV (n)		20	6	14	**0.042***
OCR (n)		16	9	7	**0.763**
Type of strabismus; n (%)	Esotropia	31 (63)	16 (67)	15 (60)	**0.769**
	Exotropia	18 (37)	8 (33)	10 (40)	

LMA: Laryngeal mask airway, OTE: Orotracheal intubation, BMI: Body mass index, PONV: Postoperative nausea or vomiting, OCR: Oculocardiac reflex, SD: Standard deviation, min: Minute, *p<0.05

spontaneously in 6 cases. Both groups had statistically similar distributions (p=0.763). PONV was found in 6 patients in the LMA group and 14 cases in the OTE group, and the difference was statistically significant (p=0.042).

The preoperative degrees of deviation of the cases in the LMA group ranged between 12-50 ΔD, with a mean of 28.48 ΔD. At the end of the first postoperative month, the degree of deviation ranged between 0-11 ΔD, with a mean of 1,2 ΔD. The preoperative and postoperative degrees of deviation in the LMA group were statistically different (p=0.001) (Table 2).

The preoperative degrees of deviation of the cases in the OTE group ranged between 20-55 ΔD, with a mean of 31.50 ΔD. At the end of the first postoperative month, the degree of deviation ranged between 0-13 ΔD, with a mean of 1,5 ΔD. The OTE group's preoperative and postoperative degrees

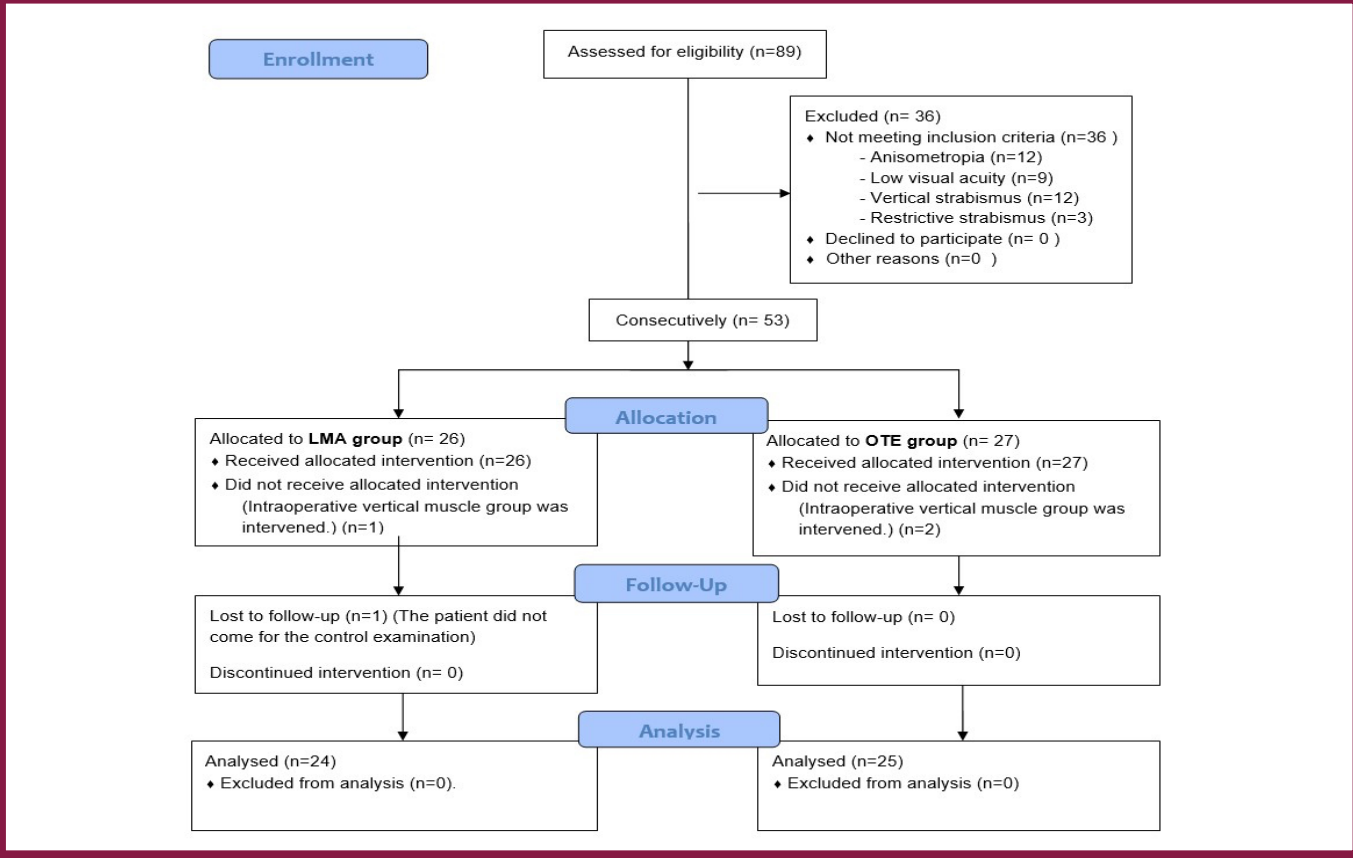

Figure 1. CONSORT flow diagram of the study participants
OTE: Orotracheal intubation, LMA: Laryngeal mask airway

Table 2. Evaluation of deviation angles in the postoperative 1st month

		LMA-group (n=24)	OTE-group (n=25)	p
The deviation angle before surgery (ΔD)	Mean ± SD	28.48±8.54	31.50±8.88	**0.135**
Median (min/max)	30 (12-50)	30 (20-55)		
The deviation angle after surgery (ΔD)	Mean ± SD	1.20±1.98	1.50±2.53	**0.784**
Median (min/max)	0 (0-11)	0 (0-13)		
	p	**0.001****	**0.001****	
The corrected deviation angle after surgery (ΔD)	Mean ± SD	-27.28±7.70	-30.00±7.95	**0.125**
Median (min/max)	-27 (-39/-12)	-30 (-42/-20)		

LMA: Laryngeal mask airway, OTE: Orotracheal intubation, ΔD: Prism diopter, SD: Standard deviation, **p<0.01

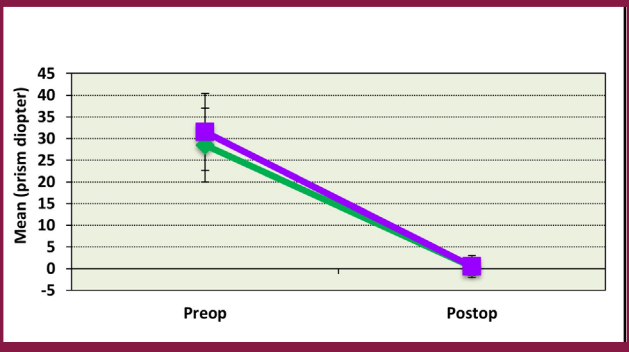

Figure 2. Distribution of deviation angles by groups one month after surgery

LMA: Laryngeal mask airway, OTE: Orotracheal intubation, Preop: Preoperative period, Postop: Postoperative period

of deviation were statistically different (p=0.001) (Figure 2). One patient in the LMA group and two patients in the OTE group had a degree of deviation than 10 ΔD at the end of the postoperative first month. There was no statistically significant difference between the groups regarding preoperative and postoperative deviation angles, the decrease in postoperative deviation angle measurements (Table 2).

Discussion

In ophthalmic surgeries, as in many other surgical procedures, anesthetists and surgeons use the technique and approach used to treat their patients. There is currently no consensus, particularly in strabismus surgery. Some surgeons prefer NMA to perform strabismus surgery, mainly while doing the Forced duction test. They are not affected by muscle tone fluctuations caused by changing the anesthetic type and depth (7). However, some clinicians do not opt for NMA. Migliorini et al. (5) studied the effects of the inhalation agent sevoflurane and desflurane in 42 patients undergoing strabismus surgery without NMA. They found that desflurane increased ocular deviation substantially more than sevoflurane. No study in the literature investigated the effect of employing NMA on the outcomes of strabismus surgery. According to the present study, the use of NMAs in strabismus surgery anesthetic did not affect the operative outcome, which is the first in this area.

Strabismus surgery rectifies the shift in the visual axes, give single binocular vision, and achieve a fair physical appearance. Several elements influence the success of the surgery. Patients with the same degree of strabismus may respond differently to the same amount of surgical correction. This indicated that the degree of deviation or surgery amount (operated muscle) is not the sole factor affecting strabismus surgery. As a result, the inability to predict the outcome of strabismus surgeries becomes a significant issue. The globally approved scales given by the American Academy of Ophthalmology are frequently used to guide the amount of muscle intervention to be made in strabismus surgeries (8). Because the values in the scales are often organized according to the preoperative deviation angles, full correction may not be possible after surgery. The influence of alterations in ocular muscle tone, which occurred with two distinct anesthetic types, on postoperative deviation angles was explored in this study, and no difference in postoperative deviation angle remission was found between the NMA (OTE) and the NMA-free (LMA) groups.

Many factors influence the degree of deviation in the postoperative period, including age, refractive problems, decreased visual acuity, type and duration of strabismus, preoperative deviation angles, surgeon experience, and how the suture is passed through the sclera (9,10,11). Although most strabismus surgeries are operated under general anesthesia, eligible and compatible adult patients can be operated on with local or topical anesthetic (2,12). Because all the patients in our study were children (aged between 2 and 14), they were all operated on under general anesthesia by the same surgeon using the same procedure. Esotropia was found in 63% of the patients, while exotropia was found in 37%, with a similar distribution between the two groups. Patients with a corrected visual acuity of greater than 0.8 were also included in the study, excluding most factors that could alter the surgical outcome. While the rates of decrease in deviation angles were similar in both groups in the postoperative 1st-month follow-up, only three (3.4%) patients had a value over the predicted (<10 ΔD) deviation angle. The three patients who did not have the expected outcome were over eight and had a preoperative deviation angle of more than 40 ΔD. Kampanartsanyakorn et al. (10) also presented the first surgical results of 304 patients with horizontal strabismus (61.5% esotropia, 38.5% exotropia), reporting that success rates were low in patients aged over six and in patients with preoperative deviation angles greater than 30 ΔD. As a result, we were unable to acquire the desired postoperative values in our patients with advanced age (>8 years) and sizeable preoperative deviation angles (>40 ΔD) in our study.

LMA is regularly and safely used for pediatric anesthesia (13,14). LMA in pediatric anesthesia was considered an alternative to tracheal intubation in the early 2000s; however, with the advent of next-generation LMAs such as I-gel and Cobra perilaryngeal airway, LMA has now become the preliminary choice in general anesthetic applications. Gulati et al. (15) compared the use of LMA and OTE in

strabismus surgery in 2004. They found that the LMA group had lower intraocular pressure increase and greater PONV due to LMA-induced gastric inflation. Nevertheless, PONV was shown to be lower in the LMA group in our study. The lack of a gastric drainage canal and inhalation medications utilized for anesthesia maintenance in first-generation classical LMAs could cause this paradox. In our study, we employed propofol (TIVA) to maintain anesthesia in the LMA group, and we used the new generation I-gel LMA with gastric drainage channel as the LMA. As a result, we observed statistically considerably less PONV than the OTE group, where anesthesia was maintained with an inhalation drug. Kranke et al. (16) also reported that when propofol was utilized for strabismus surgery anesthesia, there was less PONV than inhalation agents.

Some authors report that propofol has the same effect as metoclopramide, an antiemetic agent, at sub-hypnotic doses (17). The mechanism of this effect is not precise. It has been postulated to be an antagonist at the 5HT3 receptor. Other reports suggest that the anti-emetic effect of propofol is due to modulation of the subcortical pathways (16,17). In many recent reports, propofol should be the first choice among anesthetic agents, especially since it prevents the development of PONV in strabismus surgery of pediatric patients (18).

OCR is identified with a reduction in heart rate of more than 15% or the onset of a new arrhythmia. During the traction and manipulation of the extraocular muscles in strabismus surgery, OCR can develop at rates ranging from 14 percent to 90 percent (19). OCR was detected at a rate of 33% in our investigation, with no differences between the groups. Aydın et al. (20) presented the results of 86 patients who underwent pediatric strabismus surgery and reported that 34% of OCR developed. The same report also stated that the group utilizing NMA developed statistically more negligible OCR. In our study, the NMA group (OTE) developed quantitatively more minor OCR, although there was no statistical significance. In this study, rocuronium was used as NMA. It is well known that rocuronium has vagolytic effects (21). We think that this effect reduced the development of OCR in our study. Addionatally, since some studies reported that the OCR was statistically lower in patients receiving premedication, we did not administer premedication to any patient in our study to not impair the standardization of our research (20).

Study Limitations

The most significant limitation of the study is the small number of cases and one-month postoperative follow-up. The success of strabismus surgery was also assessed in terms of anatomical success in our research. Because the patients were not followed up for an extended period, functional benefits such as binocularity and stereopsis were removed from the evaluation. Thus, randomized controlled studies with a larger sample size and more extended follow-up periods (>12 months) are required.

Conclusion

The tone changes in the eye muscles with the use of NMAs in strabismus surgery anesthesia caused no changes in the postoperative deviation angles or the surgical result.

Acknowledgments

We want to thank the eye clinic that operated and measurements on the cases in our study for their essential efforts.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the national ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Okmeydanı Training and Research Hospital (approval no: 943, approval date: August 7, 2018).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Evaluation of Radiopaque Jaw Lesions in a Turkish Population: A Retrospective Study

Türk Toplumunda Radyoopak Çene Lezyonlarının Değerlendirilmesi: Retrospektif Bir Çalışma

Dursun Ali Şirin[1], Celalettin Topbaş[1], Şeyda Erşahan[2], Yelda Erdem Hepşenoğlu[2]

[1]*İstanbul Medipol University Faculty of Dentistry, Department of Endodontics, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Hamidiye Faculty of Dentistry, Department of Endodontics, İstanbul, Turkey*

ABSTRACT

Background: Radiopaque lesions are frequently found in the periapical region. The diagnosis and treatment of these lesions can be challenging to the dentist. The present study presents the similar radiographic features of the lesions to help the clinician narrow the differential diagnosis and to aid in treatment planning. This study aims to evaluate the frequency and distribution of radiopaque lesions in a Turkish population.

Materials and Methods: This retrospective study was conducted at the Department of Endodontics, Hamidiye Faculty of Dentistry, University of Health Sciences Turkey, İstanbul, Turkey. Data was obtained from digital panoramic images taken between 2018-2021. A total of 2.002 patients were included. The incidence of specific radiopaque lesions, like idiopathic osteosclerosis, condensing osteitis, odontoma, cementoblastoma, cementoosseous dysplasia, and fibrous dysplasia was evaluated with relation to gender. In addition to these, the frequency of pulp stones was also evaluated. Descriptive statistics and the chi-square test were used to evaluate the data.

Results: Of the 1.912 patients diagnosed with radiopaque lesions, 960 (50.2%) were female and 952 (49.8%) were male. Radiopaque lesions were determined on 106 (5.5%) panoramic radiographs. While idiopathic osteosclerosis was found in 58 (3%), condensing osteitis was found in 33 (1.7%), odontoma was found in 1 (0.1%), cementoblastoma was found in 1 (0.1%), cemento-osseous dysplasia was found in 10 (0.5%) and fibrous dysplasia was found in 3 (0.2%) patients. Moreover, a pulp stone was found in 142 (7.4%) patients. No statistically significant difference was found between genders in any of the lesions ($p>0.05$), except for condensing osteitis ($X^2=0.024$).

Conclusion: The most common radiopaque lesions in the study were idiopathic osteosclerosis and condensing osteitis, while the least common was cementoblastoma and odontoma.

Keywords: Jaw, radiopaque lesions, radiographic images

ÖZ

Amaç: Periapikal bölgede radyoopak lezyonlar sıklıkla bulunmaktadır. Bu lezyonların teşhisi ve tedavisi diş hekimi için zorlayıcı olabilir. Bu lezyonlar benzer görüntüleme özelliklerine sahip olabilir ve bu çalışmada klinisyenin ayırıcı tanıyı daraltmasına ve hasta tedavisini planlamasına yardımcı olmak için temel radyografik özellikler sunulmaktadır. Bu çalışmada, Türk popülasyonunda radyoopak lezyonlarının sıklığı ve dağılımının incelenmesi amaçlandı.

Gereç ve Yöntemler: Radyoopak çene lezyonlarının bu retrospektif çalışması Türkiye'de Sağlık Bilimleri Üniversitesi, Hamidiye Diş Hekimliği Fakültesi Endodonti Anabilim Dalı'nda yapılmıştır. Veriler 2018'den 2021'e kadar dijital panoramik radyografi görüntülerinden alınmıştır. Toplam 2002 hasta dahil edilmiştir. Bu çalışmada cinsiyete ek olarak idiyopatik osteoskleroz, kondensing osteitis, odontoma, sementoblastoma, semento-osseöz displazi ve fibröz displazi gibi radyoopak lezyonların görülme sıklığı değerlendirildi. Bunlara ek olarak pulpa taşı sıklığı da değerlendirildi. Verilerin değerlendirilmesinde tanımlayıcı istatistikler ve ki-kare testi kullanıldı.

Bulgular: Radyoopak lezyon tanısı alan 1,912 hastanın 960'ı (%50,2) kadın, 952'si (%49,8) erkekti. Yüz altı (%5,5) panoramik radyografide radyoopak lezyonlar tespit edildi. Elli sekizinde (%3) idiyopatik osteoskleroz, 33'ünde kondensing osteitis (%1,7), 1'inde

Address for Correspondence: Şeyda Erşahan, University of Health Sciences Turkey, Hamidiye Faculty of Dentistry, Department of Endodontics, İstanbul, Turkey
Phone: +90 532 405 40 88 E-mail: seydaersahan@hotmail.com **ORCID ID:** orcid.org/0000-0002-0354-5108

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ÖZ

odontoma (%0,1), 1'inde sementoblastoma (%0,1), 10'unda sementoosseoz displazisi (%0,5) ve 3'ünde fibröz displazi (%0,2) bulundu. Dahası 142'sinde pulpa taşı (%7,4) bulundu. Kondensing osteitis (X^2=0,024) dışında hiçbir lezyonda cinsiyetler arasında istatistiksel olarak anlamlı fark bulunmadı (p>0,05).

Sonuç: Çalışmada en sık radyoopak lezyonlar idiyopatik osteoskleroz ve kondens osteitis iken en az görüleni sementoblastoma ve odontoma idi.

Anahtar Kelimeler: Çene, radyoopak lezyonlar, radyografik görüntüler

Introduction

Numerous radiopaque and radiolucent lesions are seen in the jaws. An accurate diagnosis is mandatory for correct treatments of dental infections (1). Granulomas, radicular cysts and periapical abscesses are the most common radiolucent lesions that are seen during radiographic examination (1). On the other hand, radiopaque lesions are observed around the apex of the teeth, too and their correct diagnosis is important, as they can be of odontogenic or non-odontogenic origin (2).

Numerous previous studies (3), including studies from Turkey (4), have investigated the frequency of radiolucent lesions. Although the epidemiological profile of radiopaque lesions has been investigated in different populations in the past, few studies have examined such lesions in Turkey (5,6,7). Although the incidence of radiopaque lesions in the jawbone is less than radiolucent lesions (8,9); investigating the epidemiological data of these lesions is very important in the correct diagnosis. Such studies could help the clinician carry out a differential diagnosis for these lesions. Since the geographical distribution may cause differences, there is a need to examine this issue in our country. Therefore, the aim of the present study was to retrospectively investigate the incidence of radiopaque lesions in a Turkish population by using panoramic radiography.

Materials and Methods

This retrospective study was conducted by evaluating 1.912 randomly selected digital panoramic radiographic images of patients who came to University of Health Sciences Turkey, Hamidiye Faculty of Dentistry, Department of Endodontics between 2019-2021. Nine-hundred sixty radiographs belonged to females and 952 to male subjects (female: male ratio 1:1). Male and female patients aged 18-65 years were included in the study. The study sample consisted Turkish patients with permanent dentition. Any radiographs with primary or mixed dentition were excluded. This study is approved by the Institutional Review Board of University of Health Sciences Turkey (E-46418926-050.99-89060). As this study is a retrospective study, written consent was not obtained from the participants. Images were obtained by using Orthopantomograph OP200 D (Instrumentarium Dental, Tuusula, Finland), operating at 70 kVp and 4.9 mA with 14.1 s exposure time in standard mode. Digital panoramic images were evaluated at different times by a researcher with five years of experience in digital panoramic image evaluation. In this study, the presence of radiopaque lesions on panoramic radiographs was evaluated retrospectively. Among these lesions, idiopathic osteosclerosis, condensing osteitis, odontoma, cementoblastoma, cementoosseous dysplasia and fibrous dysplasia (FD) were evaluated. Other lesions were not included in the study. In this study, the relationship between the presence of radiopaque lesions and gender was also investigated.

Statistical Analysis

All statistical analyses were performed using the SPSS 27.0 statistical software (SPSS Inc., IL, USA). Frequency and percentage were used for descriptive statistics. The chi-square test was used to compare the qualitative data. The result was considered statistically significant when the p-value was <0.05.

Results

Of the 1.912 patients included in the study, 960 (50.2%) were female and 952 (49.8%) were male.

In this study, radiopaque lesions were found in 106 (5.5%) of 1912 patients. Sixty-four (3.3%) of these lesions were found in women and 42 (2.1%) were found in men. Idiopathic osteosclerosis (Figure 1a) was seen in a total of 58 (3.0%) patients, 30 (3.1%) female and 28 (2.9%) male (Table 1). There was no difference between men and women in terms of idiopathic osteosclerosis (p>0.05) (Table 1).

Cementoosseous dysplasia (Figure 1b) was seen in 10 (0.5%) patients; 8 (0.8%) female and 2 (0.2%) male. There was no statistical difference between men and women in terms of cementoosseous dysplasia (p>0.05) (Graphic 1 and Table 1). Odontoma (Figure 1c) was found in 1 male patient (0.1%) and cementoblastoma in 1 female patient (0.1%). There was no difference between men and women in terms of odontoma (p>0.05) (Graphic 1 and Table 1).

Moreover, a pulp stone (Figure 1c) was found in 142 (7.4%) patients. No statistically significant difference was found between genders.

Condensing osteitis was seen in 33 (1.7%) patients, 23 (2.4%) female and 10 (1.1%) male (Figure 1d). Condensing osteitis lesions were found to be higher in women compared to men ($p<0.05$) (Graphic 1 and Table 1).

Cementoblastoma was seen in 1 (0.05%) patient; 1 (0.1) female and 0 (0.1%) male. There was no statistical difference between men and women in terms of cementoblastoma ($p>0.05$) (Graphic 1 and Table 1).

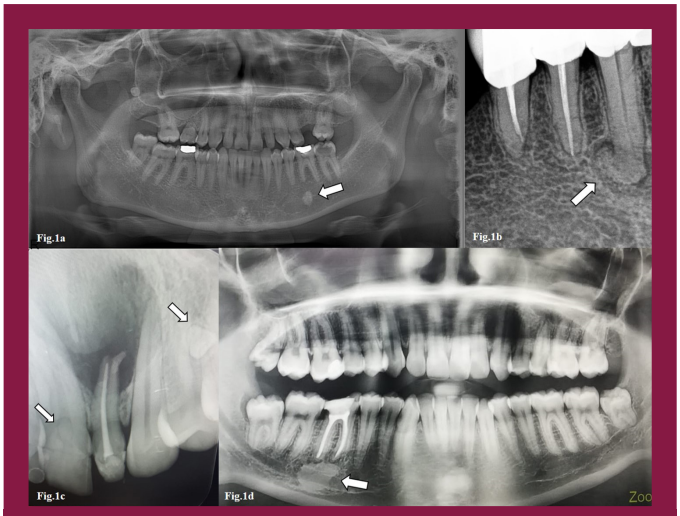

Figure 1. A composite figure of commonly seen radiopaque lesions is given in Figure 1. Fig.1a) An example of idiopathic osteosclerosis; Fig.1b) An example of cementoosseous dysplasia; Fig.1c) An example of odontoma and pulp stone; Fig.1d) An example of condensing osteitis

FD was seen in 3 (0.2%) patients; 2 (0.2%) female and 1 (0.1%) male (Graphic 1). There was also no statistical difference between men and women in terms of FD ($p>0.05$) (Graphic 1 and Table 1). It was remarkable that there was no statistically significant difference in the incidence of radiopaque lesions between the genders, except for condensing osteitis ($p>0.05$).

Discussion

This retrospective study found the prevalence of radiopaque jaw lesions in a Turkish population to be 5.5%. This value is in the same range with the literature, which is between 2% and 9.7% (8,9,10,11).

The present study demonstrated that idiopathic osteosclerosis was the most common radiopaque lesion in the Turkish population. Idiopathic osteosclerosis is a term used to describe a highly dense area of bone that is not associated with an inflammatory, neoplastic or systemic disease. They do not have any obvious etiological agents (12). They are usually asymptomatic, they do not cause cortical expansion, and they are detected incidentally on routine radiographs (13,14). The frequency of idiopathic osteosclerosis (3%) in this investigation falls within the range found by other studies, which vary from 1.96 to 7.6% (12,13,15,16). Although Miloglu et al. (16) and Avramidou et al. (15) found that the incidence of idiopathic osteosclerosis was higher in women, Williams and Brooks (13), Halse and Molven (12) and Dedeoğlu and Arıkan (17) did not find any differences between the genders in their study. In our study, no statistical difference was found between the genders.

Graphic 1. The distribution of radioopaque jaw lesions in a Turkish population

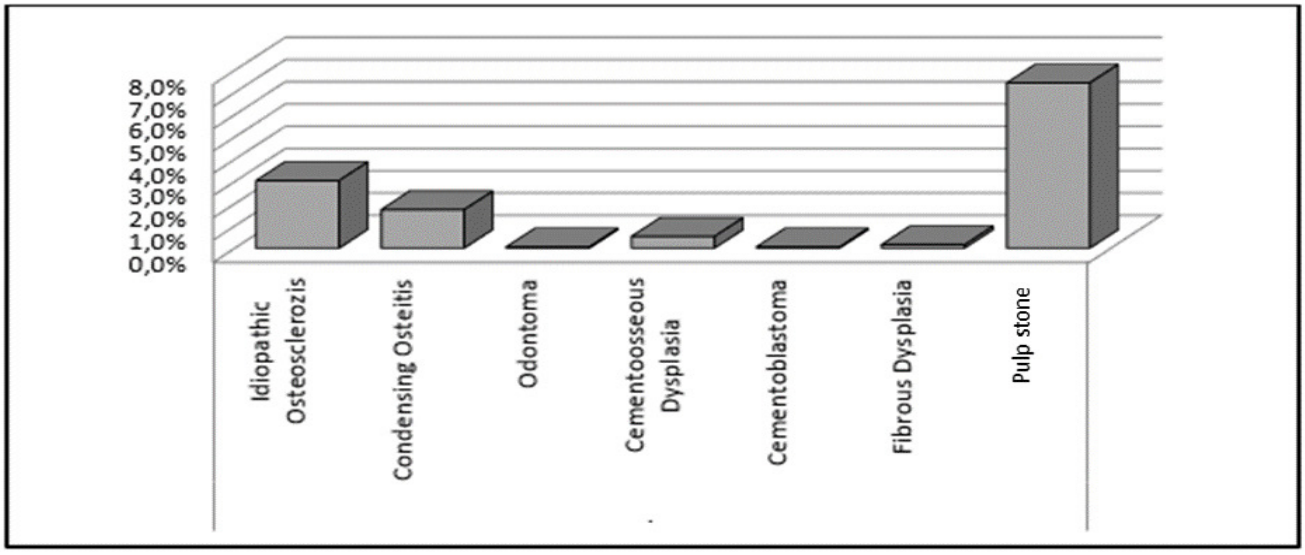

Table 1. The distribution of subgroups of radiopaque lesions according to gender

		Female		Male		p	
		n	%	n	%		
Idiopathic osteosclerosis	(-)	930	96.9%	924	97.1%	0.815	X^2
	(+)	30	3.1%	28	2.9%		
Condensing osteitis	(-)	937	97.6%	942	98.9%	**0.024**	X^2
	(+)	23	2.4%	10	1.1%		
Odontoma	(-)	960	100.0%	951	99.9%	0.498	X^2
	(+)	0	0.0%	1	0.1%		
Cementoosseous dysplasia	(-)	952	99.2%	950	99.8%	0.059	X^2
	(+)	8	0.8%	2	0.2%		
Cementoblastoma	(-)	959	99.9%	952	100.0%	1.000	X^2
	(+)	1	0.1%	0	0.0%		
Fibrous dysplasia	(-)	958	99.8%	951	99.9%	1.000	X^2
	(+)	2	0.2%	1	0.1%		
Pulp stone	(-)	886	92.3%	884	92.9%	0.637	X^2
	(+)	74	7.7%	68	7.1%		

X^2: Chi-square test (Fischer's Exact)

There is no apparent need for any intervention in idiopathic osteosclerosis (12).

The second most common lesion in the present study was condensing osteitis. They are focal sclerotic lesions that develop at the root apex due to low-grade chronic apical infection in teeth with a nonvital pulp (13,18). There are many factors in the etiology of condensing osteitis such as deep caries, extensive restorations, inadequate root canal treatments, orthodontic forces, dental eruption, and fixed prostheses (19). It appears as a well-defined dense radiopaque halo around the apices of a nonvital tooth. The incidence of condensing osteitis was found between 4-8% in studies conducted (17,19,20). The prevalence of condensing osteitis was found 1.7% in this study, in line with the previous studies. Although Williams and Brooks (13), Halse and Molven (12) and Verzak et al. (21) did not find any differences between the genders in their study, Miloglu et al. (16) found that the incidence of condensing was higher in women. Similarly, a significant difference was found between the genders in the present study. Root canal treatment or extraction has been recommended for the tooth with this lesion (22). After endodontic treatment the sclerotic area usually returns to normal bone density in nearly 70% of cases, however changes to the alveolar bone may still remain visible on radiographs even after extraction of the associated tooth (22).

Cemento-osseous dysplasia is a lesion of unknown origin, consisting of the periodontal ligament and cement or cement-like tissues in the areas of the jaw bones with tooth roots (23). The lesions occur periapically in vital teeth, which distinguishes them from condensing osteitis. These lesions can be seen as radiolucency, mixed, and radiopaque on radiographs, according to its stages. The radiolucent lesions seem like periapical infections; but, the tooth is vital. The mixed and radiopaque lesions have a well-defined radiolucent rim around the radiopaque areas (24). At this stage, the clinician must be careful not to make a misdiagnosis (25). Diagnosis is often difficult, and clinical and histological examinations may be required for accurate diagnosis. Taking a biopsy of cemento-osseous dysplasia lesions is contraindicated as the avascular cemental masses are susceptible to osteomyelitis (24). The prevalence of cemento-osseous dysplasia is between 0.24% and 5.9% (25,26). One study found that cemento-osseous lesions were seen more often in women (27). The incidence of cemento-osseous lesion was found as 0.5% in this study. Similarly, it was observed with a higher incidence in women, although not significant. No treatment is required and only periodic examination by radiographs are enough. Biopsy, extraction, periodontal surgery, and implant surgery are contraindicated due to the increased risk of osteomyelitis (24).

FD is a benign disease characterized by the replacement of normal bone by abnormally mineralized fibrous tissue. FDs appear radiolucent in the early period, while they appear radiopaque and typically as ground glass in the later period (23). In FD, which is known to be continuous with the surrounding bone, the margins are not clear, and they expand (28). In two previous studies, the incidence of FD

was found to be 1.87% and 0.09, respectively (17,29). In our study, the incidence was found as 0.2%. The management of FD is conservative. Lesions not causing deformity can be followed. Treatment is necessary only for problems caused by a local increase in the size of the bone. Partial resections can be performed for lesions involving large and multiple bones and deformities (30).

Odontomas are very common benign odontogenic tumors. The lesion includes abnormally developed dentin and enamel components. Trauma, infection, hereditary anomalies, and odontoblastic alterations can be responsible for the etiology of odontomas. They usually appear as small or multiple radiopaque lesions on panoramic radiographs. Odontomas are generally asymptomatic, but they can cause the delay of the eruption of a tooth or tooth retention. The incidence of odontoma is accepted to be between 0.14-0.8% (31). In our study, the incidence of odontoma was found to be 0.1%. Although the growth of odontomas is limited, they need to be surgically removed because of their potential of bone collapse, problems with permanent tooth eruption, and their cystic nature (32).

Cementoblastoma is a rare benign odontogenic tumor. Clinically, it presents with pain and swelling of the buccal and lingual alveolar processes. Teeth are usually vital (33). It can be seen as a round radiopaque mass surrounded by a radiolucent rim on radiographs. Sometimes, root resorption and tooth displacement can be seen with this lesion (33). Prevalence of cementoblastoma was found in 0.1% of patients in the current study. If diagnosed in the early period, root canal treatment and apical resection are sufficient for treatment, while extraction may be considered in advanced cases (34).

Pulp stones are a form of pulp calcifications. But, the etiology of pulp stones is not clear. Pulp irritations such as long-term mastication forces, occlusal trauma, bruxism, periodontal pathology, orthodontic forces, and chronic pulp inflammation can be accounted for in the etiology (35). According to a systematic review, the frequency of pulp stones is about 36.5% (36), however its frequency in the Turkish population was found to be 7.4%. This difference can be explained largely by the differences between methodologies. In that previous study, only molar teeth were assessed. However, in the present study, all teeth including anteriors, premolars, and molars were evaluated. Pulp stones might be a challenge during root canal treatment and may obliterate the entrance of the canals.

Study Limitations

These results should be evaluated with caution due to the sample limitations. As the study sample was only contains the patients attending Health Sciences University, results regarding the frequency of radiopaque lesions cannot be extrapolated to the general Turkish population. Panoramic radiographs were evaluated in the present study. Due to its three-dimensional nature, CBCT has advantages over two-dimensional panoramic imaging. Since radiographs convert 3-D information into a 2-D image, lesion margins and extent cannot be rightly evaluated. Further CBCT imaging is required to assess the detailed morphological characteristics of the lesion.

Conclusion

This study showed that the prevalence of radiopacities in a Turkish population are relatively rare, occurring in 5.5% of the population. This study also demonstrated that idiopathic osteosclerosis and condensing osteitis were the most commonly seen radiopaque lesions in the Turkish population.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Ethics Committee of the University of Health Sciences Turkey, Scientific Research (E-46418926-050.99-89060).

Informed Consent: As this study is a retrospective study, written consent was not obtained from the participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.A.Ş., C.T., Concept: D.A.Ş., C.T., Ş.E., Y.E.H., Design: D.A.Ş., C.T., Ş.E., Y.E.H., Data Collection or Processing: D.A.Ş., C.T., Analysis or Interpretation: Ş.E., Y.E.H., Literature Search: Ş.E., Y.E.H., Writing: D.A.Ş., C.T., Ş.E., Y.E.H.

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

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Intrahepatic Cholestasis and Adverse Perinatal Outcomes in the Third Trimester: A 10-year Case-control Study

Üçüncü Trimesterde İntrahepatik Kolestaz ve Olumsuz Perinatal Sonuçlar: 10 Yıllık Bir Olgu Kontrol Çalışması

Cem Yener, Cenk Sayın, Esra Altan Erbilen, Sinan Ateş, Füsun Varol

Trakya University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology, Edirne, Turkey

ABSTRACT

Background: To evaluate the perinatal outcomes in women whom developed intrahepatic cholestasis of pregnancy (ICP).

Materials and Methods: Medical records of 76 patients who were followed up in a tertiary center due to ICP between January 2010 and December 2019 were evaluated retrospectively. Women with ICP (n=76) and age matched controls (n=228) were included to our study. Bile acid (BA) values could be reached in 42 of 76 patients.

Results: There was no significant difference in terms of family history, fetal gender, or the presence of meconium in the amniotic fluid between the groups (p>0.05) except cesarean rates were significantly higher in ICP group (p<0.001). The median gestational weeks at delivery, fetal weight and Apgar scores at the 1st- and at the 5th-minutes in the ICP group were significantly lower than those in the controls (p<0.05). Gestational weeks at delivery was similar in women with BA values above or under 40 µmol/L (p>0.05).

Conclusion: ICP has important fetal implications. There is an increased risk for poor fetal outcomes, including preterm delivery and fetal demise. Therefore, close follow-up and meticulous observation is indispensable.

Keywords: Intrahepatic cholestasis, neonatal outcome, pregnancy, ursodesoxycholic acid

ÖZ

Amaç: Bu çalışmadaki amacımız gebeliğinde intrahepatik kolestaz (ICP) gelişen kadınlarda perinatal sonuçları değerlendirmektir.

Gereç ve Yöntemler: Ocak 2010 ile Aralık 2019 tarihleri arasında üçüncü basamak bir merkezde ICP nedeniyle izlenen 76 hastanın tıbbi kayıtları geriye dönük olarak değerlendirildi. ICP'si mevcut olan kadınlar (n=76) ve aynı yaştaki kontroller (n=228) çalışmaya dahil edildi. Safra asidi (SA) değerlerine 76 hastanın 42'sinde ulaşılabildi.

Bulgular: Gruplar arasında aile öyküsü, fetal cinsiyet ve amniyotik sıvıda mekonyum varlığı açısından anlamlı fark yoktu (p>0,05), ama sezaryen oranları ICP'li grupta anlamlı olarak yüksekti (p<0,001). ICP'li grubunda doğumdaki ortalama gebelik haftası, fetal ağırlık ve 1. ve 5. dakika Apgar skorları kontrollere göre anlamlı derecede düşüktü (p<0,05). SA değerleri 40 µmol/L'nin üzerinde veya altında olan kadınlarda doğumdaki gebelik haftaları benzerdi (p>0,05).

Sonuç: ICP'nin önemli fetal etkileri vardır. Erken doğum ve fetal ölüm dahil olmak üzere kötü fetal sonuçlar için artan risk mevcuttur. Bu nedenle yakın takip ve titiz gözlem vazgeçilmezdir.

Anahtar Kelimeler: İntrahepatik kolestaz, neonatal sonuç, gebelik, ursodeoksikolik asit

Introduction

Intrahepatic cholestasis of pregnancy (ICP) occurs due to the dysfunction of the membrane transport system of the hepatocyte and bile duct epithelium that provide bile excretion. It may occur due to genetic, autoimmune, metabolic, hormonal, environmental factors and as a result of some drugs or infections (1). Some mutations in the multidrug resistance 3 (MDR3/ABCB4) gene was observed, which is also found in progressive familial intrahepatic cholestasis (2).

Address for Correspondence: Cem Yener, Trakya University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Perinatology, Edirne, Turkey
Phone: +90 532 748 61 80 E-mail: drcemyener@hotmail.com **ORCID ID:** orcid.org/0000-0002-3976-4492
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The worldwide incidence of ICP ranges from 0.1% to 1.5% (3,4), but is more common in multiple pregnancies and in Latin-American or Araucanian-Indian pregnant women (5,6). It is the most common liver disease in pregnant women, that is observed in the second and third trimesters of pregnancy, often after the 30th week (7).

Clinically, widespread peripheral itching is observed, especially in the palms and soles, increasing at night, so causing insomnia and mental distress. It is associated with increased serum liver transaminase and bile acid (BA) values. The clinical symptoms occur approximately 3 weeks before the laboratory findings, but usually regress within 48 hours after birth (8). Jaundice appears in 10% to 25% of patients. Some may also develop abdominal pain, diarrhea, and steatorrhea. Coagulopathies can develop due to a decrease in vitamin K absorption (9). Total BA concentration may increase up to 10 to 100 times. Cholesterol levels and usually serum alkaline phosphatase (ALP) levels increases. Hyperbilirubinemia occurs, but serum levels seldomly exceed 4-5 mg/dL. Serum transaminase levels may be normal or moderately increased, rarely exceeding 250 IU/L. Other dermatological diseases should be investigated, if liver enzymes are in normal limits. Abdominal ultrasonography may be necessary to detect gallstones and related obstructions. The absence of proteinuria and hypertension allows it to be differentiated from preeclampsia, or from acute viral hepatitis with low serum transaminase levels. Asymptomatic chronic hepatitis C increases the incidence of cholestasis (10). Even though, ICP has a benign character that regresses at the end of delivery without causing maternal serious morbidity and mortality, unlike the maternal condition, fetal morbidity and mortality increases. Maternal BA cross the placenta and may accumulate in the fetus and amniotic fluid, which carries notable risk for the fetus (11). Transplacental gradients facilitate fetal clearance of BA in normal pregnancies, albeit are reversed in this disease and this causes an accumulation of BA in the fetus and amniotic fluid (12). Hence, ICP may cause preterm birth, abnormal intrapartum fetal heart tracings and sudden intrapartum fetal death (13,14).

Our aim was to investigate the possible adverse fetal and maternal effects of ICP in our population in women that developed the disease in the 3rd trimester of pregnancy. In addition, our objective was to evaluate the likely relationship between increased BA levels and adverse outcomes.

Material and Methods

The medical histories of all pregnant women with ICP (n=76) that had given birth at the Perinatology Division of Trakya University Faculty of Medicine, between 1st of January 2010 and 31st of December 2019, and their neonatal outcomes were obtained from the hospital records and reviewed retrospectively with the approval of the Trakya University's Human Ethics Committee (no: 2020/230) in accordance with the Declaration of Helsinki.

We included patients meeting the following criteria in our study group.

• Generalized itching without a dermatological pathological condition.

• Laboratory findings supporting intrahepatic cholestasis [increased serum alanine transaminase (ALT) and aspartate transaminase (AST), and if available BA levels].

• Normal appearance of the liver and gallbladder by an ultrasonographic observation.

• Absence of active hepatitis, confirmed by HBsAg and Anti HCV testing.

Pregnant women having multiple pregnancies (n=13), congenital malformations (n=4), chromosomal abnormalities (n=1), systemic disease (n=5) and recurrence of cholestasis (each woman was included only one time) (n=4) were excluded from the study.

The control group was randomly selected from pregnant women who did not have any chronic disease and made their regular obstetric visits in our maternal and fetal unit, whom had uneventful pregnancies. Eligible control women (n=228) had a singleton pregnancy, the fetus in a cephalic presentation, without congenital malformations and no obstetric disorders requiring preterm induction. The control population was matched for maternal age (one year more or less), date of delivery (same calendar year), the same parity, the same mode of delivery history, did not have ICP and had normal liver transaminase levels. In order to increase our study power, three women with low-risk pregnancies were enrolled as controls for each ICP case.

After the diagnosis of ICP was made, all women were consulted and the systemic examinations were performed by a gastroenterologist. Topical emollients, antihistamines and ursodesoxycholic acid (Ursofalk®, Ali Raif İlaç San. A.Ş, İstanbul) at a dose of 300 mg three times a day were applied to all women having ICP.

Fetal and maternal outcomes and laboratory characteristics were compared in women with ICP and the controls. BA values could be reached in 42 patients. In a further analysis, women were divided into 2 groups according to values under (n=25) or above (n=17) 40 µmol/L, and the outcomes were also compared in these subgroups.

Statistical Analysis

K-S test was performed to examine the normality agreement of the distributions of the measurements of the patients.

After the test, it was determined that their distribution did not show normality. Descriptive statistics in the study

are given as median and IQR. Mann-Whitney U test was used to analyze the measurements according to patient groups. Logistic regression analysis was performed to determine the risk factors affecting the state of being sick. Risk levels (odds β) were determined according to the 95% confidence interval (Upper-Lower). Differences were defined as significant when p<0.05. SPSS 25 (Statistical Package for Social Science, Chicago, II, USA) Windows package program was used for statistical analysis.

Results

During the study period, 6.896 women were admitted for delivery. The incidence of ICP was 1.1%. The mean age of the pregnant women with ICP and controls was 27 (25-33).

There was no significant difference in terms of fetal gender, presence of meconium in the amniotic fluid, or family history of ICP (p<0.05). Women who had ICP in their previous pregnancies had a higher rate of ICP than those who did not experienced ICP previously (p<0.001). Cesarean rates were significantly higher in the ICP group (p<0.001). Indications for cesarean in ICP group was previous cesarean section (%56), scheduled cesarean delivery (33%) and non-reassuring fetal heart rate pattern/labor dystocia (13%). Induction of labor was performed to 44.7% (n=34) of women with ICP, compared to 11.8% (n=27) of the controls (p<0.001). Cesarean rates during labor were not observed significantly different between ICP group 13.3% (n=6) with the controls 12.1% (n=10) (p=0.557). Preterm delivery was significantly higher in the ICP group (39.4% vs. 3.9%, p<0.001) (Table 1).

Itching was the most common symptom in patients with ICP (100%). Medications relieved pruritus in 72 (94%) women. Other common symptoms were nausea (76%) and poor appetite (68%), respectively. Significantly lower gestational weeks at delivery, subsequently lower fetal birth weight, height, head circumference and additionally lower Apgar scores at the 1st-and at the 5th-minutes were observed in ICP group compared to the controls (p<0.001) (Table 2). There was no significant difference between the groups in terms of postpartum hemoglobin and hematocrit levels, postpartum hemorrhage or maternal transfusion need (p=0.299) (Table 2).

In terms of BA values, there was no statistically significant difference between the 2 groups, except for the high ALT levels observed in patients with BA ≥40 μmol/L (p=0.032) (Table 3).

Discussion

This retrospective case control study describes the feto-maternal outcome of obstetric cholestasis in a referral center of Thrace Region of Turkey. We found significantly lower gestational weeks at delivery, fetal weight and Apgar scores at the 1st-and at the 5th-minutes in the ICP group. No significant difference was observed between women with BA values above or below 40 μmol/L in terms of gestation weeks at birth, fetal weight and Apgar scores.

The incidence of ICP is between <1% and 27.6% worldwide. In the United States, incidence rates range from 0.32 percent to 5.6 percent. The incidence in Europe ranges from 0.5 to 1.5 percent, with the highest rates in Scandinavia. The incidence of ICP in our cohort was 1.1%, which is compatible with previous studies (1,2,3,4,5). The typical symptom of ICP is mild to unbearably itchy. It

Table 1. Maternal characteristics and obstetric outcomes of women with ICP and the controls

		Controls (n=228)	ICP (n=76)	p
Maternal age, years [median (IQR)]		27 (25-33)	27 (25-33)	1
Delivery weeks, n (%)	**>37 weeks**	219 (96.2%)	46 (60.6%)	**<0.001**
	<37 weeks	9 (3.9%)	30 (39.4%)	
Route of delivery, n (%)	**Vaginal**	139 (61%)	31 (49.7%)	**<0.001**
	Cesarean	89 (39%)	45 (51.3%)	
Induction of labor, n (%)	**Applied**	27 (11.8%)	34 (44.7%)	**<0.001**
Fetal gender, n (%)	**Female**	103 (45.2%)	35 (46%)	0.858
	Male	125 (54.8%)	41 (54%)	
Meconium-stained fluid, n (%)	**Positive**	29 (12.7%)	8 (10.5%)	0.687
Parity, n (%)	**Nulliparous**	99 (43.5%)	33 (43.4%)	0.989
	Multiparous	129 (56.5%)	43 (56.6%)	
Familial history of ICP, n (%)	**Positive**	2 (0.8%)	1 (1.3%)	0.169
Personal history of previous ICP, n (%)	**Positive**	0	10 (13.2%)	**<0.001**

ICP: Intrahepatic cholestasis of pregnancy, IQR: Interquartile range

usually starts on the palms and soles and worsens at night. Right upper quadrant pain, nausea, loss of appetite, sleep deprivation, or steatorrhea may occur. These symptoms usually develop in the late second or third trimester. In our study group itching was the most common symptom. Topical emollients, antihistamines and ursodesoxycholic acid (300 mg three times a day) are the treatments of choice in these patients. These medications relieved pruritus 72 out of 76 women in our population. However, there are opposing views in the literature. While, some believed

Table 2. Fetal and maternal outcomes and laboratory characteristics of women with ICP and the controls [values are presented as (median IQR)]

	Controls (n=228)	ICP (n=76)	p
Gestational age at birth, weeks	38 (38-39)	36 (35-37)	**<0.001**
Fetal birth weight, grams	3.335 (3.070-3.650)	2.850 (2.577-3.132)	**<0.001**
Fetal height, cm	50 (49-52)	48 (46-50)	**<0.001**
Fetal head circumference	35 (33-35)	34 (33-35)	**<0.001**
Apgar score, 1st-min	9 (9-9)	8 (8-9)	**<0.001**
Apgar score, 5th-min	10 (10-10)	10 (9-10)	**<0.001**
Aspartate transaminase, IU/L	16 (14-21)	110 (64.5-162.5)	**<0.001**
Alanine transaminase, IU/L	10 (8-14)	95.5 (63-138)	**<0.001**
Platelet, 10^3/μL	202 (174-267)	214.5 (165-266)	0.932
Postpartum hematocrit, g/dL	35.1 (32.8-36.9)	34.9 (31.4-36.4)	0.708
Postpartum hemoglobin, g/dL	11.6 (10.7-12.6)	11.5 (10.5-12.05)	0.801
Prothrombin time, s	11.5 (11.2-12.1)	11.7 (11.6-13)	0.263
Activated partial thromboplastin time, s	23.6 (22.4-24.6)	23.8 (22.4-25.95)	0.326
Postpartum hemorrhage, n (%)	11 (4.8%)	4 (5.2%)	0.774
Maternal transfusion, n (%)	4 (1.7%)	1 (1.3%)	0.299

ICP: Intrahepatic cholestasis of pregnancy, IQR: Interquartile range

Table 3. Fetal outcomes and laboratory characteristics according to the bile acid levels [values are presented as (median IQR)]

	Bile acid value		p
	<40 μmol/L (n=25)	≥40 μmol/L (n=17)	
Maternal age, years	27 (21-35)	32 (23-35)	0.370
Gestation age at birth, weeks	37 (34-38)	37 (36-39)	0.368
Fetal birth weight, grams	2.700 (2.550-3.040)	2.870 (2.610-3.100)	0.290
Fetal height, cm	48 (45-50)	48 (46-50)	0.447
Fetal head circumference, cm	34 (33-35)	35 (34-35)	0.116
Apgar score, 1st-min	8 (8-9)	9 (7-9)	0.733
Apgar score, 5th-min	9 (9-10)	9 (9-10)	0.392
Aspartate transaminase, IU/L	82 (60-160)	146 (110-186)	0.105
Alanine transaminase, IU/L	78 (57-108)	132 (100-174)	**0.032**
Platelet, 10^3/μL	246 (176-268)	246 (126-290)	0.751
Hematocrit, g/dL	33.4 (29.8-36.4)	32.8 (30.6-35)	0.832
Hemoglobin, g/dL	11 (9.1-12.1)	10.6 (10.3-11.8)	0.944
Prothrombin time, s	12.4 (11.8-13.2)	13.1 (11.4-13.4)	0.832
Activated partial thromboplastin time, s	30.3 (25.2-33.6)	26.6 (25.8-29.7)	0.274
Postpartum aspartate transaminase, IU/L	26 (14-40)	46 (24-48)	0.097
Postpartum alanine transaminase, IU/L	18 (15-32)	36 (18-50)	0.162

IQR: Interquartile range

that this treatment improved the perinatal outcomes, some others thought it has no effect on adverse perinatal outcomes (15). PITCHES trial assessed perinatal outcome in ICP-affected pregnancies. The study evaluated the effect of ursodeoxycholic acid versus placebo and found that ursodeoxycholic acid treatment has no considerable effect on diminishing adverse perinatal outcomes (16). Since we administered ursodeoxycholic acid to all women with ICP in our cohort of patients, we could not comment on the effect of the treatment on perinatal outcomes, but we might even think that ICP per se have already some negative effects on some maternal and fetal outcomes such that despite lower gestational weeks at delivery, fetal weight or Apgar scores in women with ICP, not to commence any medication might have worsened these outcomes. Besides, a recent Cochrane review found the effectiveness of ursodeoxycholic acid to ameliorate pruritus, and also argued that the evidence for some adverse fetal outcomes like fetal distress and stillbirth were uncertain and unclear, due to serious limitations in study designs and imprecision (17). In our 10-year study period, no stillbirths occurred in the ICP group, but 3 patients who were previously diagnosed with ICP by another medical center admitted to our institute with stillbirth. Of those, two were at the 38th and the other was at the 39th weeks of pregnancy [BA level (68 µmol/L) could be reached in one out of three patients]. These patients were not under routine control after a diagnosis of ICP and were also not receiving ursodeoxycholic acid. All reported that they were asked to be hospitalized by their obstetricians. Nevertheless, they either denied to be hospitalized or use of ursodeoxycholic acid. We can consider using ursodeoxycholic acid, because, it is not only effective in reducing pruritus and improving maternal liver condition, but it might also bring some benefits for the fetal outcomes, since no fetal losses occurred in patients whom were hospitalized patients receiving ursodeoxycholic acid.

There is no consensus regarding the obstetric management of patients diagnosed with ICP. In the study in which 70 cases were examined, they were interviewed weekly about their symptoms. All were actively managed according to a standard protocol of delivery before 38 weeks and obstetric outcomes were recorded. Based on these results, it was thought that active management policies might result in increased intervention and related complications, but this should be balanced against possible reductions in perinatal mortality (18). In our daily practice patients with ICP were hospitalized to diagnose and to identify possible conditions like preterm birth and fetal well-being. Modified biophysical profile (cardiotocographic examinations and amniotic fluid levels by ultrasound) was applied twice weekly. We discharge the patients if the fetal conditions are stable by a biophysical profile score $\geq$8, without and other accompanying problems like preterm labor or conditions such as uterine contractions. Thereafter, the patients were recommended close monitoring. Patients were observed weekly to check for the fetal status after the 32nd weeks, and twice weekly after the 36th weeks. At each visit modified biophysical profile was performed and if the ICP women having the deterioration of the symptoms like worsening of itching or clinically apparent jaundice then the serum ALT, AST and BA levels were reevaluated. We have planned delivery at 38 weeks or at diagnosis, if diagnosed later. The American College of Obstetricians and Gynecologists endorses active management protocols for ICP (19). In recently published committee opinion, delivery was suggested that if the levels are above 100 µmol/L at 36 0/7 weeks of gestation. If the BA levels are less than 100 µmol/L, it is recommended to deliver between 36 0/7-39 0/7 weeks. Likewise, in Australia and France, obstetricians support induction of labor for patients with ICP at 37-38 completed weeks of pregnancy (20,21). However, The Royal College of Obstetrics and Gynaecologists does not support routine active management of ICP-affected pregnancies (22). ICP carries the main risk for the fetus. Out of 352 pregnancies diagnosed with ICP, 23 (7%) were complicated by intrauterine death and preterm delivery occurred in 133 (38%) of them. Eighteen of the 20 individual intrauterine deaths occurred after 37 weeks. Itching begins earlier in pregnancies complicated by spontaneous prematurity (23). An activation of the oxytocin receptor pathway has been shown to occur during ICP. This event appears to be the result of a cholic acid-mediated increase in oxytocin receptor expression (24). As in some other previous studies, we found significant differences in gestational age at delivery in women with ICP and the controls (2,3,4,5,6,7,9). In addition, fetal birth weight and Apgar scores were observed significantly lower in ICP group. On the other hand, ICP does not adversely affect the mother as it severely does to the fetus. In our study, no significant difference was found in terms of postpartum hemorrhage and postpartum transfusion.

Whilst, there are studies which show the association of ICP with increased meconium-stained amniotic fluid, in present study we didn't observe statistically difference in terms of meconium-stained amniotic fluid between study groups (12,25). We hypothesized that this is due to our active management policy for ICP. Stillbirth occurred in 45 (0.83%) of 4936 ICP cases and 519 (0.32%) of 163 947 control pregnancies in a meta-analysis. In singleton pregnancies, stillbirth was associated with the maximum total bile acid concentration, but not with alanine aminotransferase. For singleton pregnancies, the prevalence of stillbirth was 3 in 2310 cases of ICP in women with serum total bile acids less than 40 µmol/L, 4 in 1412 cases with total bile acids of 40-99 µmol/L, and 524 for bile acids of 100 µmol/L or more 18 cases were detected (26). In our 10-year study period, no stillbirths occurred in ICP group. Therefore, after a diagnosis of ICP, close monitoring of the women should be warranted.

Due to the retrospective design, we could not find the BA levels of all patients. Di Mascio et al. (8) observed a

negative relationship between increasing levels of BA with birth weight and Apgar scores. However, we found similar gestational weeks at delivery, and fetal weights between in those having BA levels <40 μmol/L and ≥40 μmol/L.

Study Limitations

Our study limitations were firstly subgroup analysis was performed on small population and secondly our retrospective study design, as well potential bias about efficacy of ursodeoxycholic acid in reducing of stillbirth.

Conclusion

ICP is associated with adverse fetal outcomes. Hence, close follow-up and meticulous observation might have roles in the prevention of some serious outcomes like stillbirth.

Ethics

Ethics Committee Approval: Reviewed retrospectively with the approval of the Trakya University Human Ethics Committee (no: 2020/230) in accordance with the Declaration of Helsinki.

Informed Consent: The study was designed retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Evaluation of CD47 Expression in Solid Pancreatic Tumors Diagnosed with Endosonography Guided Fine Needle Aspiration Biopsy

Endosonografi Eşliğinde İnce İğne Aspirasyon Biyopsisi ile Tanı Konulan Solid Pankreas Tümörlerinde CD47 Ekspresyonunun Değerlendirilmesi

Nurcan Ünver[1], Ganime Çoban[2], Nurhan Şahin[2], Zuhal Gücin[2], Hakan Şentürk[3], Dilek Sema Arıcı[4]

[1]*Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey*

[2]*Bezmialem Vakıf University Faculty of Medicine, Department of Pathology, İstanbul, Turkey*

[3]*Bezmialem Vakıf University Faculty of Medicine, Department of Gastroenterology, İstanbul, Turkey*

[4]*Biruni University Faculty of Medicine, Department of Pathology, İstanbul, Turkey*

ABSTRACT

Background: CD47, which is also known as integrin-associated protein, is a membrane protein of the immunoglobulin superfamily. Its expression was shown to be elevated in hematologic and many solid organ malignancies like pancreatic tumors.

Materials and Methods: The materials of 80 patients diagnosed with endosonography (EUS)-guided fine needle aspiration biopsy (FNAB) and 42 patients diagnosed after resection were evaluated retrospectively. EUS guided FNAB specimens of all cases and slides prepared from blocks that had been selected from the subsequently obtained resection materials were stained with CD47 immunohistochemical staining. According to the CD47 expression level, it was divided into two groups as low and high, and the results were compared with clinicopathological and prognostic factors.

Results: Eighty patients (male=36, female=44, mean age=61.32 years) were included in our study. In 80 EUS biopsy material, 53 (66.75%) cases were diagnosed with adenocarcinoma and this diagnosis was confirmed in resected patients. We found that 32 of 80 patients who underwent EUS-guided FNAB and 32 of those who underwent resection had positive staining with CD47. Considering high and low staining levels with CD47, our study showed a significant difference between high CD47 expression and disease-free survival in resection materials ($p<0.005$), but did not find a significant relationship between other clinicopathological prognostic factors.

Conclusion: Although high CD47 expression levels were not detected in most EUS biopsy samples, it was observed that high CD47 expression had a negative prognostic effect on disease free survival.

Keywords: Pancreatic cancer, endoscopic ultrasonography, CD47 protein, prognoses

ÖZ

Amaç: İntegrin ile ilişkili protein olarak da bilinen CD47, immünoglobulin süper ailesinin bir membran proteinidir. Pankreas tümörleri gibi hematolojik ve birçok solid organ malignitesinde ekspresyonunun arttığı gösterilmiştir.

Gereç ve Yöntemler: Endosonografi (EUS) eşiliğinde ince iğne aspirasyon biyopsisi (FNAB) ile tanı alan 80 hasta ve rezeksiyon sonrası tanı alan 42 hastanın materyalleri retrospektif olarak değerlendirildi. Tüm olguların EUS biopsi örnekleri ve rezeksiyon materyallerinden seçilen bloklardan hazırlanan kesitler CD47 immünohistokimyasal boyası ile boyandı. CD47 ekspresyon düzeyine göre düşük ve yüksek olarak iki gruba ayrıldı ve sonuçlar klinikopatolojik ve prognostik faktörlerle karşılaştırıldı.

Bulgular: Çalışmamıza 80 hasta (erkek=36, kadın=44, yaş ortalaması=61,32 yıl) dahil edildi. Seksen EUS biyopsi materyalinde 53 (%66,75) olguya adenokarsinom tanısı konuldu ve bu tanı rezeke edilen materyallerde doğrulandı. EUS eşliğinde FNAB uygulanan

Address for Correspondence: Nurcan Ünver, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Clinic of Pathology, İstanbul, Turkey
Phone: +90 505 216 00 18 E-mail: pat.dr.nurcanunver@gmail.com **ORCID ID:** orcid.org/0000-0001-7392-6099

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ÖZ

80 hastanın 32'sinde ve rezeksiyon yapılan hastaların 32'sinde CD47 ile pozitif boyanma saptandı. CD47 ile yüksek ve düşük boyama düzeyleri göz önüne alındığında, çalışmamız rezeksiyon materyallerinde yüksek CD47 ekspresyonu ile hastalıksız sağkalım arasında anlamlı bir fark olduğunu gösterdi (p<0,005), ancak diğer klinikopatolojik prognostik faktörler arasında anlamlı bir ilişki bulunmadı.

Sonuç: EUS biyopsi örneklerinin çoğunda yüksek CD47 ekspresyon düzeyleri saptanmamasına rağmen, yüksek CD47 ekspresyonunun hastalıksız sağkalım üzerinde olumsuz prognostik etkisi olduğu gözlenmiştir.

Anahtar Kelimeler: Pankreatik kanser, endoskopik ultrasonografi, CD47 protein, prognoz

Introduction

According to statistical research, pancreatic cancer ranks third in cancer-related mortality and its rates have been increasing gradually over the years (1). The most common solid tumors of the pancreas are pancreatic ductal adenocarcinomas. Prognostic factors such as clinical stage, depth of tumor invasion, lymph node metastasis, and histological grade are important in the evaluation. These tumors are associated with quite high recurrence and distant metastasis rates, even after curative treatment with surgical resection and subsequent adjuvant chemotherapy. In the resectable group, survival time is usually shorter than two years, even after postoperative adjuvant chemotherapy. This highlights the need for research on potential solutions that can be curative in the early diagnosis and treatment of these tumors.

Endosonography (EUS) guided fine needle aspiration biopsy (FNAB) plays an important role in the grading and histological diagnosis of pancreatic and peripancreatic lesions (2). Evaluations made using EUS were shown to have high diagnostic impact and reliability in cases of pancreatic adenocarcinoma (2,3) with this method, both solid-semisolid and cystic lesions of the pancreas can receive a faster and more reliable diagnosis, accelerating the treatment decision for the patient.

CD47 is a membrane protein of the immunoglobulin superfamily. CD47 is a widely expressed cellular receptor well known for its immunoregulatory functions. By interacting with its ligands such as signal regulatory protein α and thrombospondin-1, it modulates cellular phagocytosis by macrophages, transmigration of neutrophils and activation of dendritic cells, T-cells and B-cells (4). CD47 expression was determined to be high in most solid organ malignancies (5,6,7,8,9,10). Since CD47 secretion in the cancer cell membrane would inhibit the phagocytic activity of immune cells; it is associated with a poor prognosis in many solid organ malignancies (8,11,12,13). Accordingly, the suppression of CD47 results in tumor inhibition. Some studies have shown that various types of cancer express high levels of CD47 to escape from the immune system. Based on these studies, CD47 is currently considered a prominent target in cancer therapy.

Pancreatic carcinomas are highly destructive tumors that progress rapidly. Although there are few studies in the literature on solid pancreatic tumors, longer disease-free survival can be expected for these devastating tumors as the number of relevant studies increases and new antitumorigenic immunotherapy agents are developed. In this study, it was aimed to evaluate the CD47 expression in determining treatment planning and prognostic factors in pancreatic tumors diagnosed with EUS-FNAB and resected afterwards, and to compare CD47 expression levels with clinical and prognostic parameters.

Material and Methods

Endoscopic and Pathological Evaluation

EUS-FNAB was planned for 80 cases with a preliminary diagnosis of pancreatic solid tumor. The endoscopy of the patients was performed using the Fujinon EG 530WR endoscopy device in the endoscopy unit of our hospital. All patients were starved for 6 hours before endoscopy, and the endoscopy procedure was performed after local pharyngeal xylocaine anesthesia. The cell blocks and slide preparations prepared from the samples taken were sent to the pathology laboratory. The pathological diagnosis were made under light microscopy and immunohistochemical evaluations.

Biopsy materials of 42 cases diagnosed with EUS biopsy and subsequently resected in our hospital were extracted from the block and side archives of the pathology laboratory and re-evaluated. CD47 staining was made immunohistochemically to EUS biopsy materials and sections of blocks selected from tumor resections.

Tissue Immunohistochemistry Staining and Pathological Evaluation

New sections were obtained from EUS cell blocks and resection materials and mounted onto polylysine slides, which were then stained with the CD47 (Abcam CD47 antibody ab3283, Cambridge, UK) monoclonal antibody using the Ventana immunohistochemical staining device.

All slides were evaluated for CD47 expression using a Nikon light microscope with H&E slides in a controlled manner. In the evaluation of CD47; cytoplasmic and membranous brown staining in the cells were considered and the extent of expression was also graded besides its intensity. The extent of CD47 expression in the cells was graded as; "0" if there was no staining, "1" if there was staining in up to 10% of the cells, "2" if there was staining in 11-25% of the cells, and "3" if there was staining in 50% or more. Accordingly, those with staining graded as 0 and 1 were evaluated within the low CD47 expression group ($CD47^{low\ exp}$) and those with staining graded 2-3 were evaluated within the high CD47 expression group ($CD47^{high\ exp}$), thus categorizing the cases into two groups.

CD47 expression was evaluated in 80 EUS samples. At the same time, both EUS biopsy materials and tumor resection materials were evaluated for CD47 low and high expression in 42 cases. Statistically, CD47 expressions were compared. Also, the post-treatment clinical follow-up records of the patients were reviewed to record the known survival times. It was also investigated whether or not the states of CD47 expression were correlated with survival times.

Statistical Analysis

The chi-squared test was used to analyze the association between candidate CD47 expression and clinicopathological characteristics of pancreatic lesions. Survival curves were evaluated using the Kaplan-Meier method, and differences between survival curves were tested by the log-rank test. Only significantly different variables in univariate analysis were included in the multivariate analysis. Statistical signifcance was based on two-tailed tests at $p<0.05$. SPSS 22.0 (IBM Corp.) and GraphPad Prism 6 (San Diego, CA, USA) software was used for statistical analyses and graphical representation.

Results

Eighty cases diagnosed with EUS-guided FNAB in our hospital were included in the study. The mean age of the 80 patients included in this study was 61.32 years. The minimum age was 16 years and the maximum age was 87 years. Out of 80 patients diagnosed with EUS-guided FNAB in our hospital, the diagnoses of 42 patients who were operable were confirmed at resection material. Of the 42 resection patients, 33 had a final diagnosis of pancreatic ductal adenocarcinoma, 7 had a final diagnosis of neuroendocrine tumor, and 2 had a final diagnosis of solid pseudopapillary neoplasm in their reports. The pathological tumor stage was pT3 in 25 cases, pT2 in 8 cases, pT1 in 6 cases, and pT4 in 3 cases. Of the resection patients, 25 demonstrated lymph node metastasis, 31 perineural invasion, and 26 lymphovascular invasion. All clinicopathological parameters are summarized in Table 1.

CD47 staining was observed in 32 of 80 patients who underwent EUS-guided FNAB and 32 of 42 patients who underwent resection (Table 2).

When CD47 staining levels are evaluated Of the 42 resection materials, 22 showed $CD47^{high\ exp}$ (52.38%) (Figure 1a, b) and 10 showed $CD47^{low\ exp}$ (23.82%) (Figure 2a, b) staining. Out of a total 80 EUS- FNAB materials, 19 showed

Table 1. Clinicopathological features of patients

Operation	**(n)**	**(%)**
EUS-FNAB	80	100
Pancreatic resection	42	52.5
Age (16-87)		
Median	61.32	-
Sex		
Male	36	45
Female	44	55
Diameter (1-13 cm)		
Median	3.95	-
Pathology		
Adenocarcinoma	53	66.25
NET	19	23.75
SPPN	3	3.75
GIST	3	3.75
Adenosquamous	2	2.5
Pathologic grade		
pT1	6	14.29
pT2	8	19.05
pT3	25	59.52
pT4	3	7.14
CD47 positivity		
EUS-FNAB	32 (n=80)*	42.10
Pancreatic resection	32 (n=42)**	76.90
Lymphovasculer invasion		
Yes	26	61.9
No	16	38.0
Perineural invasion		
Yes	31	73.8
No	11	26.19
Lymph node metastasis		
Yes	25	59.52
No	17	40.48

*Number of all cases belonging to EUS-FNAB, **Number of cases to resection materials, EUS: Endosonography, FNAB: Fine needle aspiration biopsy, NET: Neuroendocrine tumor

CD47$^{high\ exp}$ (23.75%) (Figure 3a, b) and13 showed CD47$^{low\ exp}$ (16.25%) (Figure 4a, b). 50% of the cases with resection materials in the CD47$^{low\ exp}$ group and 62.5% of the cases in the CD47$^{high\ exp}$ group had grade 2 tumors (p=0.884) (Table 2). Neither the resection material nor the EUS materials were painted with CD47 in any of the solid pseudopapiller neoplasm.

Our study showed that increased CD47 expression in resection materials. It was observed that as CD47 staining level increased in patients who underwent resection for pancreatic cancer, disease-free survival time decreased. When the levels of tumor CD47 expression in the resection materials were compared with survival times, a statistically significant relationship was determined between these two parameters (p<0.005) (Figure 5).

Discussion

The most common solid tumors of the pancreas are pancreatic ductal adenocarcinomas. Pancreatic ductal adenocarcinoma is a highly destructive tumor with a five-year survival rate lower than 5% (14).The EUS guided FNAB method is widely used in the diagnoses of solid, semisolid and cystic lesions identified in the pancreas, with high accuracy rates and low morbidity and mortality rates. Its diagnostic value is particularly high for lesions of small size (2,3).

Table 2. Summary of variables and analysis results related to CD47 expression in EUS-FNAB samples and pancreatic tumors, before resection

	CD47 tumor expression			
	Positive	**Negative**	**N of patiens (%)**	**p**
pT	**32**	**10**	**42**	
1	2 (6.25%)	4 (40.00%)	6 (14.28%)	0.363
2	6 (18.75%)	2 (20.00%)	8 (19.05%)	
3	21(65.62%)	4 (40.00%)	25 (59.52%)	
4	3 (9.37%)	0 (0.00%)	3 (7.14%)	
Hystologic grade				
1	3 (9.75%)	3 (30.00%)	6 (14.28%)	0.519
2	20 (62.50)	5 (50.00%)	25 (59.52%)	
3	9 (28.12%)	2 (20.00%)	11 (15.49%)	
Lymphovascular invasion				
Yes	21 (16.00%)	5 (50.00%)	26 (61.90%)	0.236
No	11 (40.00%)	5 (50.00%)	16 (38.09%)	
Perineural invasion				
Yes	24 (75.00%)	7 (70.00%)	31 (73.81%)	0.381
No	8 (25.00%)	3 (30.00%)	11 (26.19%)	
Lymph node metastasis				
Present	20 (62.50%)	5 (50.00%)	25 (59.52%)	0.072
Absent	12 (37.50%)	5 (50.00%)	17 (40.47%)	
CD47 resection				
High exp	22 (68.75%)	0 (0.00%)	22 (52.38%)	*0.005
Low exp	10 (31.25%)	10 (23.80%)	20 (47.62%)	
Pathology				
Adenoca	30 (69.04%)	3 (30.00)	33 (78.57%)	0.194
NET	2 (4.76%)	5 (50.00%)	7 (16.66%)	
SPPN	0 (0.00%)	2 (20.00%)	2 (4.76%)	
CD47 EUS-FNAB (before resection)	**17**	**25**	**42**	
High exp	7 (41.18%)	0 (0.00%)	7 (16.66%)	0.286
Low exp	10 (58.82%)	25 (100%)	35 (83.33%)	

Data given as frequency (percentage), *chi-square test significant p-value, NET: Neuroendocrine tumor, EUS: Endosonography, FNAB: Fine needle aspiration biopsy

CD47 is a novel prognostic biomarker of certain malignant tumors. CD47 is a widely expressed cell surface protein that regulates phagocytosis, which is mediated by innate immune system cells such as macrophages and dendritic cells (15). Numerous studies in the literature have shown elevated CD47 expression in various solid organ malignancies (5,8,12,14,16). In our study, in accordance with the literature, the final diagnosis was resulted as pancreatic adenocarcinoma in most forty-two resection cases (thirty-three). Of these, 32 had positive staining with CD47. Statistically significant high CD47 expression was observed in 22 of CD47 positive stained cases.

Yuan et al. (9) in patients with hormone receptor negative breast cancer and Lascorz et al. (17) colorectal carcinomas showed that overexpression of CD47. In a study conducted by Olcucuoglu et al. (7) high CD47 expression was reported to contribute to the evaluation of bladder tumors at various stages. These studies also showed that increased CD47 expression was a poor prognostic factor (7,9,17). Moreover, studies have shown that this increased expression promotes the escape of cancer cells from phagocytosis (8,18). Majeti et al. (10) determined that cancer cells promoted tumorigenesis and metastasis in this way. Accordingly, CD47 is considered a biomarker of cancer, and its high expression is an indicator

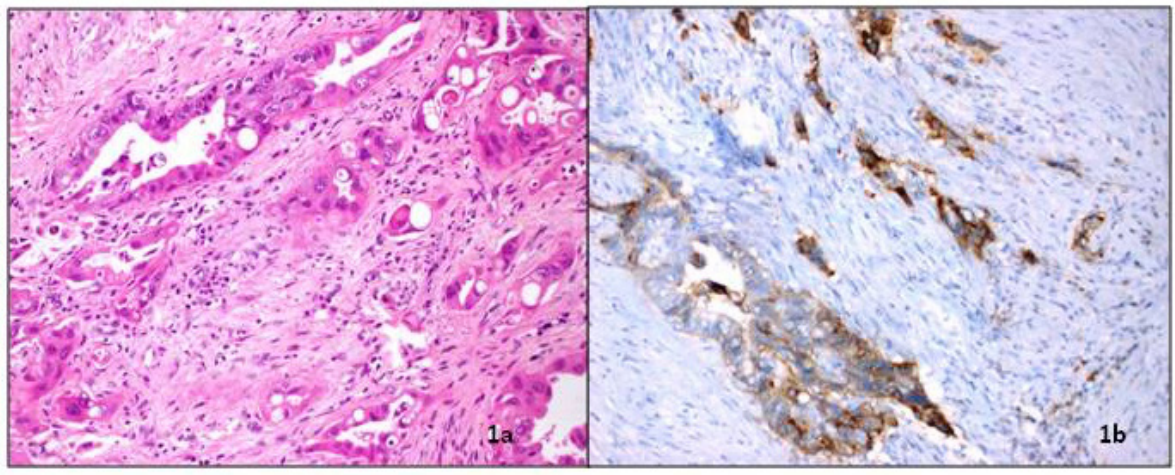

Figure 1. Pancreatic ductal adenocarcinoma (H&E section,x200) (a), CD47 high stainign (b)

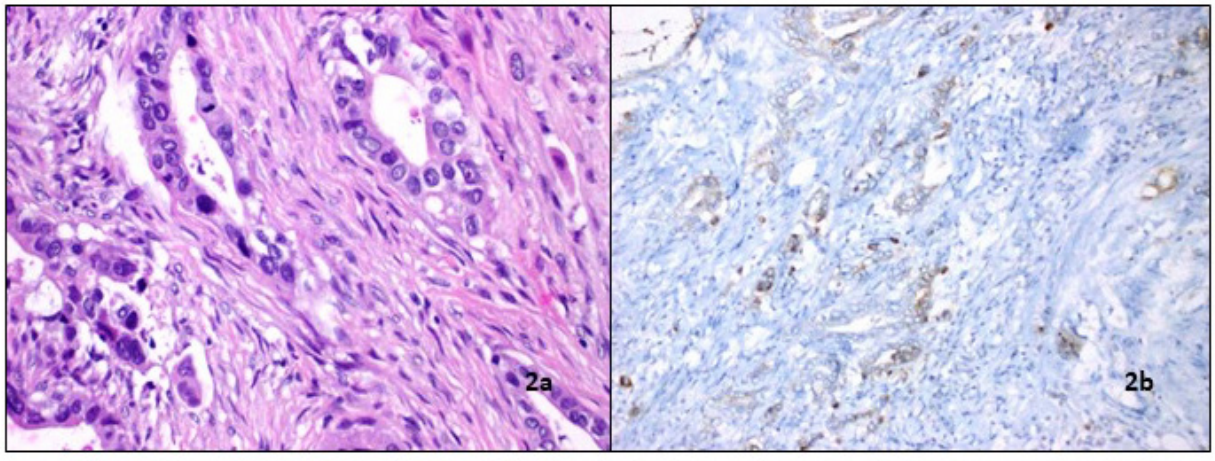

Figure 2. Pancreatic ductal adenocarcinoma (H&E section,x200) (a), CD47 low stainign (b)

of poor clinical prognosis. Edris et al. (13) demonstrated that anti-CD47 therapy inhibits the high tumor cell phagocytosis and tumor growth in cancer cell series. Similarly, Ye et al. (12) reported that CD47 could serve as a biomarker of oral precancer and cancer progression.

Patients with early-stage pancreatic cancers who undergo surgical resection and adjuvant chemotherapy have a median survival time of two years, predominantly due to the presence of micrometastatic disease in the liver that goes undetected and the consequent progression of this disease. In a study conducted by Michaels et al. (6), liver macrophages were shown to significantly stall the progression of pancreatic cancer micrometastases in a pre-clinical mouse model. The suppression effect of the macrophages was augmented by blocking CD47 on pancreatic cancer cells, leading to a decrease in metastatic burden and extending survival times. Therefore, these data support a clinical trial of CD47 blockade as an adjuvant immunotherapy for pancreatic cancer (6).

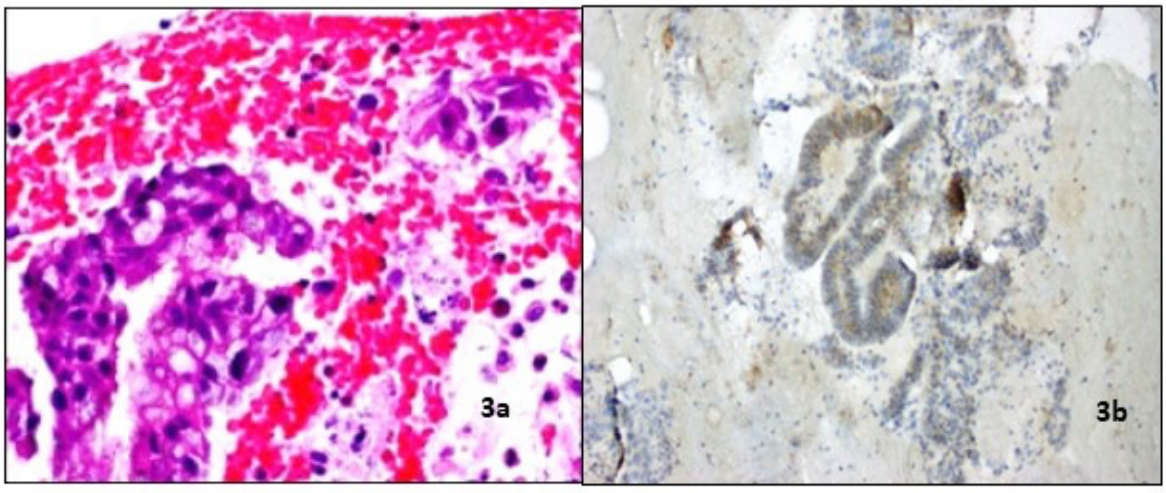

Figure 3. Cell block sections of the EUS biopsy material performed before resection of the pancreatic ductal adenocarcinoma case in figure (2a), (H&E section, x200), (b) High CD47 expression in the EUS material in the same case (respectively)

EUS: Endosonography

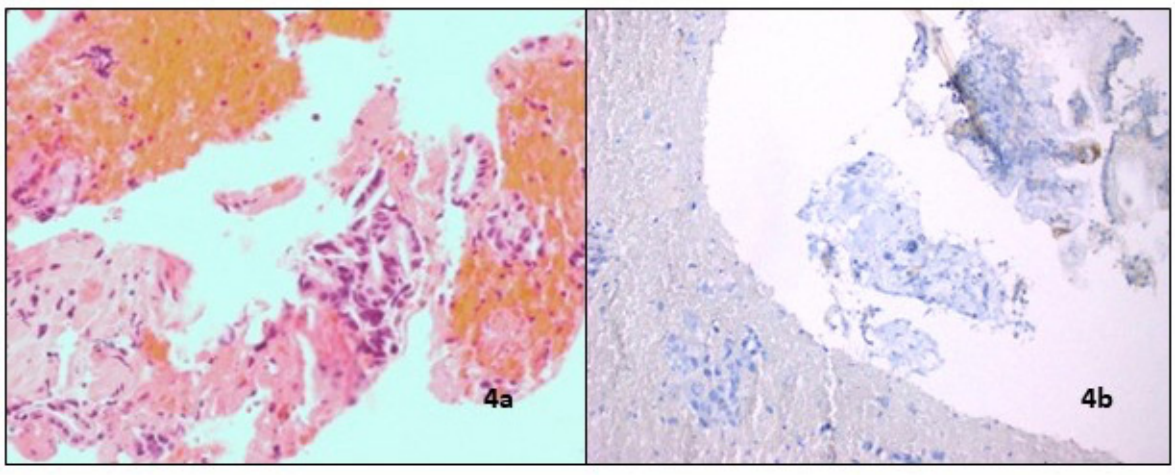

Figure 4. Cell block sections of the EUS biopsy material performed before resection of the pancreatic ductal adenocarcinoma case in figure (3a), (H&E section, x200), low CD47 expression in the EUS material in the same case (respectively) (3b)

EUS: Endosonography

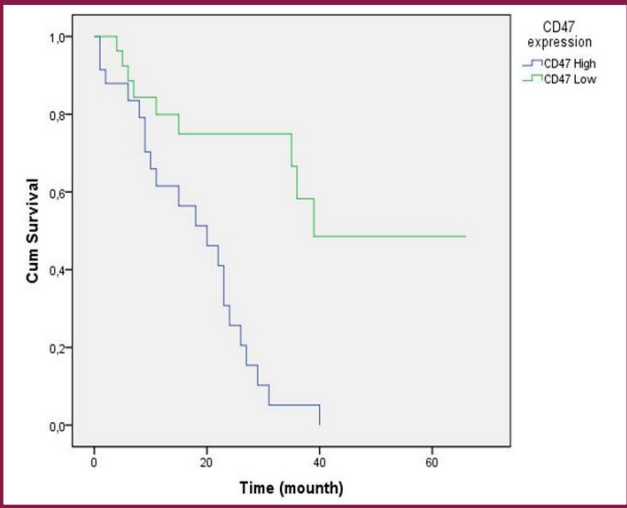

Figure 5. Kaplan-Meier survival analysis according to CD47 over expression

In order to grow and metastasize, solid tumors must escape phagocytosis with tumor-associated macrophages (19). This evidence indicates that the cell surface expression of CD47 is a common mechanism by which the cells avoid phagocytosis (20). With regard to solid organ tumors, a study done by Willingham et al. (5) showed that monoclonal antibodies that block CD47 were effective in the *in vitro* and *in vivo* treatment. Studies on experimental mouse models determined that adjuvant immunotherapy that achieved CD47 blockade resulted in increased progression free and overall survival times in resectable pancreatic cancers (6,16).

In our study, no significant staining was detected with CD47 in EUS biopsy material of eighty total cases. Evaluation of CD47 expression in EUS biopsy materials before resection was not statistically significant. This result might be explained by the limited amount of tumor cells in the cell-block materials. In this study, cell blocks obtained from 80 patients by EUS FNAB were CD47 stained, and 19 of these produced positive results. Although this number is low, these positive staining rates determined by EUS guided FNAB can guide future processes.

Study Limitations

We have some limitations in our study. Because some cell blocks contain very few tumor cells and these are the strengths of our work. Although there are a limited number of tumor cells in some cell blocks, staining detected in EUS guided FNAB may be considered important.

Pancreatic carcinomas are highly destructive tumors that progress rapidly. Although there are few studies in the literature on solid pancreatic tumors, longer disease-free survival can be expected for these devastating tumors as the number of relevant studies increases and new antitumorigenic immunotherapy agents are developed. In this study, it was aimed to evaluate CD47 expression in determining treatment planning and prognostic factors in pancreatic tumors diagnosed with EUS-FNAB and resected afterwards, and to compare CD47 expression levels with clinical and prognostic parameters.

Our study showed that increased CD47 expression in resection materials. In our study, a significant correlation was determined between elevated CD47 expression in resectable pancreatic tumors and disease free survival times. But our study did not find a significant relationship between CD47 expression levels and other clinicopathologic prognostic factors. As shown in other clinical trials, increased expression of CD47 was evaluated as a poor prognostic factor. When adjuvant immunotherapy is given and CD47 blockade is achieved, an increase in progression-free and overall survival times in resectable pancreatic cancers can be expected.

Conclusion

In our study no significant staining was detected with CD47 in EUS biopsy materials. In the resectable group, a significant correlation was found between increased CD47 expression and disease-free survival, and it was evaluated as a poor prognostic factor. As more studies on this subject increase, we think that pancreatic tumors, which are very challenging to diagnose and treat after diagnosis, may have a chance to be treated with immunotherapy according to the CD47 expression results to be applied to EUS biopsy samples before resection.

Ethics

Ethics Committee Approval: To conduct this study, ethical approval was obtained from the ethics committee of our hospital. All the applied procedures were complied with the ethical standards of human testing committee of our institution and the Helsinki Declaration. Ethical approval (study number: 12.2017/20) was obtained from the Local Ethics Committee of the Bezmialem Vakıf University of Medical School, Turkey.

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ü., N.Ş., Z.G., D.S.A, Concept: N.Ü., D.S.A, Design: N.Ü., G.Ç., Data Collection or Processing: G.Ç., N.Ş., Z.G., H.Ş., Analysis or Interpretation: N.Ü., Z.G., D.S.A., Literature Search: Z.G., D.S.A., Writing: N.Ü.

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

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ORIGINAL ARTICLE

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The Effect of COVID-19 Pandemics on Mental Health of Caregivers of Cerebral Palsy Patients

COVID-19 Pandemisinin Serebral Palsi Hastalarının Bakım Verenlerinin Ruh Sağlığına Etkisi

Koza Duman

Dr. Ayten Bozkaya Spastic Children's Hospital and Rehabilitation Center, Clinic of Physical Medicine and Rehabilitation, Bursa, Turkey

ABSTRACT

Background: The novel coronavirus disease, so-called Coronavirus disease-2019 (COVID-19), is a global public health emergency that has caused worldwide concern. The lockdown due to the COVID-19 epidemic has consequences affecting mental health on different populations in the world and in our country. This study investigated the acute and chronic phase effects of lockdown period on hopelessness, anxiety and stress of caregivers of children with cerebral palsy (CP).

Materials and Methods: The data of 31 caregivers of children with CP were included in this retrospective COHORT analysis. Those who had a history of treatment for depression, hypothyroidism and fibromyalgia, and caregivers who were found to have a Beck depression scale score above 16 points were excluded. Finally, the data of 22 caregivers were included. The data of each participant were analysed using Beck hopelessness scale, Beck anxiety inventory, and perceived stress scale (PSS) twice in timeline at least 10 months apart.

Results: There was no significant difference in the scores of the participants between the first assessment and the second assessment for the Beck anxiety inventory (p=0.971). No significant difference in scores was observed between the first and second assessments for the Beck hopelessness scale (p=0.933). The PSS showed a significant difference between the first assessment and the second assessment. Ten months after the lockdown process, the PSS scores were found to be significantly lower (p=0.001).

Conclusion: Particular attention should be paid to groups with special needs like caregivers of patients with CP during a pandemic. Various studies have shown that pandemic and lockdown may increase perceived stress levels. According to the data of this study, the perceived stress levels of CP caregivers differed significantly in the acute and chronic periods after lockdown.

Keywords: Cerebral palsy, COVID-19, stress, psychological

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) olarak adlandırılan yeni koronavirüs hastalığı, dünya çapında endişeye neden olan küresel bir halk sağlığı acil durumudur. COVID-19 salgını nedeniyle sokağa çıkma yasağı, dünyada ve ülkemizde farklı popülasyonlar üzerinde ruh sağlığını etkileyen sonuçlar doğurmaktadır. Bu çalışma, serebral palsili (SP) çocuklara bakım verenlerin umutsuzluk, kaygı ve stres üzerindeki karantina döneminin akut ve kronik faz etkilerini araştırmayı amaçlamıştır.

Gereç ve Yöntemler: Bu retrospektif COHORT analizine SP'li çocukların bakımvereni olan 31 kişinin verileri dahil edildi. Depresyon, hipotiroidi ve fibromiyalji tedavisi öyküsü olanlar ve Beck depresyon ölçeği puanı 16 puanın üzerinde bulunan bakımverenler çalışma dışı bırakıldı. Son olarak 22 bakımverenin verileri dahil edilmiştir. Her katılımcının verileri, Beck umutsuzluk ölçeği, Beck anksiyete envanteri ve algılanan stres ölçeği (ASÖ) puanları kullanılarak zaman çizelgesinde en az 10 ay arayla iki kez analiz edildi.

Bulgular: Katılımcıların Beck anksiyete ölçeği için ilk değerlendirme ile ikinci değerlendirme arasında puanları arasında anlamlı bir fark yoktu (p=0,971). Beck umutsuzluk ölçeği için birinci ve ikinci değerlendirmeler arasında puanlarda anlamlı bir fark gözlenmedi (p=0,933). ASÖ, ilk değerlendirme ile ikinci değerlendirme arasında anlamlı bir fark saptandı. Kapanma sürecinden on ay sonra ASÖ puanlarının anlamlı derecede düşük olduğu bulundu (p=0,001).

Sonuç: Pandemi sırasında SP hastalarının bakımverenleri gibi özel ihtiyaçları olan gruplara özel dikkat gösterilmelidir. Çeşitli araştırmalar, pandemi ve kapanmanın algılanan stres düzeylerini artırabileceğini göstermiştir. Bu çalışmanın verilerine göre, kapanma sonrası akut ve kronik dönemde SP bakım verenlerin algılanan stres düzeyleri önemli ölçüde farklılık göstermiştir.

Anahtar Kelimeler: Serebral palsi, COVID-19, stres, psikolojik

Address for Correspondence: Koza Duman, Dr. Ayten Bozkaya Spastic Children's Hospital and Rehabilitation Center, Clinic of Physical Medicine and Rehabilitation, Bursa, Turkey
Phone: +90 224 216 00 66 E-mail: kozaaydoseli@gmail.com **ORCID ID:** orcid.org/0000-0002-3567-6823

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Introduction

In December 2019, a deadly virus outbreak with severe pneumonia symptoms was detected in Wuhan, China (1). The epidemic, which was understood to be fatal with the findings of acute respiratory tract infection, was accepted as a pandemic by World Health Organization on March 11, 2020 (2). The first case that was reported in our country was on March 11, 2020. Following the first case notification, lockdown measures were implemented across the country on April 11 2020 to prevent the spread of the epidemic. The practice of lockdown due to the Coronavirus disease-2019 (COVID-19) epidemic has consequences affecting mental health on different segments in the world and in our country (3).

Cerebral palsy (CP) is the most common cause of motor disability in childhood. The condition, which is defined as the fixed damage detected in the brain that has not completed its development, continues to affect children worldwide. Today, two out of a thousand children receive this diagnosis, more frequently in developing countries (4). Although the damage that causes CP is a lesion of a fixed nature resulting from a single event, it has widespread consequences that affect the health and mobility of the individual (5,6). Children with a diagnosis of CP experience limitations in activities of daily living and have difficulties in mobility at different levels. In addition to motor developmental delay, conditions such as learning difficulties, epilepsy, speech and swallowing difficulties may accompany the symptoms. It is not a surprising result that the caregiver in this picture exerts maximum effort to protect his mental and physical health. There are many studies evaluating the mental health and quality of life of caregivers who run on this difficult track (7). It has been known for some time that functional disability in children affects the quality of life of mothers negatively, and that depression rates are higher than mothers of children with no physical or mental disabilities (8).

Previous studies have shown that pandemic and lockdown may increase mental health disorders and perceived stress levels (9,10,11). In our study; based on these findings, we investigate the effects of lockdown, which has negative psychological effects on all segments of the society, on hopelessness, anxiety and stress of caregivers of children with cerebral palsy.

Material and Methods

This study was approved by ethical committee with approval date and number as follows: 02/11/2021-2021/15/551. The data of the caregivers of children with CP who administered to the CP outpatient clinic of Dr. Ayten Bozkaya Spastic Children's Hospital and Rehabilitation Center in May, June and July 2020 were included. Totally, the data of 31 caregivers were included in this retrospective COHORT analysis. Among these 31 caregivers, data of those who received treatment for depression, hypothyroidism and fibromyalgia, and caregivers who were found to have a Beck depression scale score above 16 points were excluded from the study (Figure 1). Finally, 22 caregivers were included for data assessment. The first data assessment of 22 caregivers included in the study was from the files at the end of lockdown. The 2nd assessment of data of each participant who had the scores of Beck hopelessness scale (BHS), Beck anxiety inventory (BAI), and perceived stress scale (PSS) after 10 months was analysed in compared with the 1st scores.

Evaluation scales

BAI: It is a self-rating scale developed by Beck et al. (12) to determine the frequency of anxiety symptoms experienced by individuals. The scale consists of 21 items. It is a Likert type scale. Each item is scored between 0-3. Its validity and reliability in Turkey were established by Ulusoy et al. (13).

BHS: It was developed by Beck et al. (14) in 1974. The validity and reliability of the study, which was first performed by Seber et al. (15) in 1993 in Turkey, was validated with a larger sample by Durak and Palabıyıkoğlu (16). The scale consists of 20 questions. Results range from 0-20 points.

PSS: It was developed by Cohen et al. (17). It consists of 14 items in total. It is a 5-point Likert type scale. It is designed to measure the extent to which an individual perceives certain situations in his life as stressful. It is a widely used tool in studies of different populations in the United States, Canada, and Europe. The total score obtained

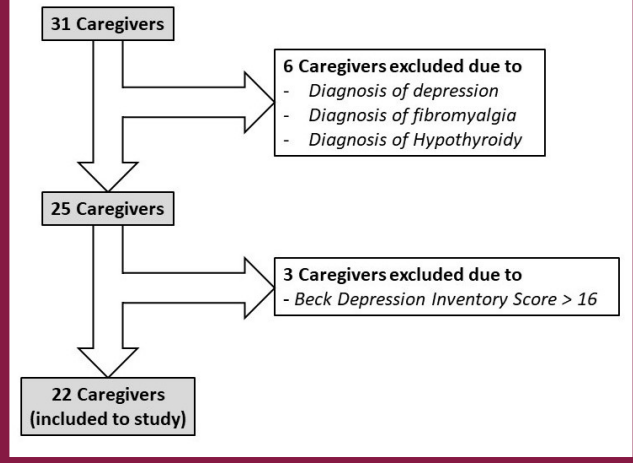

Figure 1. Flowchart

from the scale indicates the stress level of the person. A score between 11-26 indicates low stress level, a score between 27-41 indicates moderate stress level, and a score between 42-56 indicates high stress level. The validation study was conducted by Eskin et al. (18).

Statistical Analysis

All data were statistically analysed using Version 26 of SPSS (Statistical Package for the Social Sciences) software. After processing the demographic data, following the normality tests, the comparative data were evaluated with parametric/non-parametric tests according to their distribution characteristics. The "p" value was accepted as 0.05 for statistical significance.

Results

It was determined that all caregivers included in our study were women (mothers). The mean age of the caregivers included in the study was 38.45 (±6.07) years. Eleven (50%) of the participants had primary education, 10 (45.5%) had high school and 1 (4.5%) had university education. While 16 (72.7%) of the mothers have lived with their spouses, 6 (27.3%) of them have lived separately from their spouses. Eleven (50%) mothers said that they have their own income, while 11 (50%) mothers did not have their own income. It was determined that the monthly household income of 10 (45.5%) of the participant group was below 2500 TL, the monthly household income of 9 (40.9%) was between 2500-5000 TL, and the monthly household income of 3 (13.6%) was 5000 TL (Table 1).

There was no significant difference in the scores of the participants between the first assessment and the second assessment for the BAI (p=0.971). The first assessment median score was 6 (minimum: 2, maximum: 23). Similarly, in the second assessment, the median score was found to be 6 (minimum: 2, maximum: 20) (Table 2).

Similarly, no significant difference in scores was observed between the first and second assessments for the BHS (p=0.933). While the median score was determined as 2 (minimum: 0, maximum: 10) for the participants in the first scoring, the median score was found to be 2 (minimum: 0, maximum: 11) in the second assessment (Table 2).

The PSS showed a significant difference between the first assessment and the second assessment. In the second data which were recorded at least 10 months after the lockdown process, the PSS scores were found to be significantly lower (p=0.001). While the mean PSS score was found to be 23.36 (±6.29) in the first evaluation, the mean PSS score was found to be 17.41 (±5.13) in the second evaluation (Table 2).

Although the PSS score at the end of the lockdown was found to be lower in primary school graduates compared to high school graduates [primary school graduate mean score: 23.18 (±6.01), high school graduate mean score: 23.3 (±7.17)] in the first evaluation, no significant difference was

Table 1. Study group demographic data

		n	Total	%	Total (%)
Monthly household income	<2.500 TL	10	22	45.5	100
	2.500-5.000 TL	9		40.9	
	>5.000 TL	3		13.6	
Education	Primary school	11	22	50.0	100
	High school	10		45.5	
	University	1		4.5	
Living with/without spouse	Without spouse	6	22	27.3	100
	With spouse	16		72.7	
Presence of own income	None	11	22	50.0	100
	Present	11		50.0	

Table 2. Assessment results, values are given as median (minimum-maximum) or mean (± SD) according to distribution characteristics. The level of significance is p<0.05

	1st assessment	2nd assessment	p
BAI	6 (2-23)	6 (2-20)	0.971
BHS	2 (0-10)	2 (0-11)	0.933
PSS	23.36 (±6.29)	17.41 (±5.13)	**0.001**

BAI: Beck anxiety inventory, BHS: Beck hopelessness scale, PSS: Perceived stress inventory, SD: Standard deviation

observed according to education level (p=0.883). In the second evaluation, although the PSS score was found to be lower in high school graduates [mean score of primary school graduates: 17.73 (±4.08), mean score of high school graduates: 16.2 (±5.75)], no significant difference was found according to education level (p=0.529). One participant was not included in this analysis since she was the only participant with a university degree.

When the PSS scores of the participants were examined according to the presence or absence of their own income, it was seen that the participants without their own income in the first assessment have higher PSS scores [mean PSS score of those without their own income: 23.73 (±5.68), the mean PSS score of those who have their own income: 23 (±7.11)] was observed, but no statistically significant difference was found (p=0.879). Although the second assessment found that participants with their own income had a lower PSS score [mean PSS score of those without their own income: 18.27 (±5.4), mean PSS score of those with their own income: 16.55 (±4.95)], there was no significant difference according to the presence or absence of their own income (p=0.642).

Discussion

In this study, the acute and chronic effects of the COVID-19 pandemic on the mental health of caregivers of children with CP and the perceived stress effect were investigated. COVID-19 pandemic conditions have created hopelessness worlwide, causing an increase in depression and anxiety (9,19,20).

There are many studies examining the mental health and quality of life of mothers of children with cerebral palsy. It is known that functional disability in children negatively affects the quality of life of mothers, and depression rates are higher than mothers of children with no physical or mental disabilities (8,21,22). Therefore, the depression parameter, which is the focus of many studies, is the exclusion criterion in our study. Our results did not include data on depression.

It is expected that the new rules created by the pandemic conditions, the change in lifestyles and the feeling of uncertainty will increase the level of anxiety. In a meta-analysis evaluating the results of 288,830 participants in 68 studies from nineteen countries, it was found that one out of every three people had symptoms of anxiety and depression related to the pandemic. It is seen that there are conflicting results among the studies for the sub-results of the meta-analysis. It has been shown that being female, younger than 35 years old, and having financial difficulties facilitates the onset of symptoms. Although there are variations in subgroup findings in studies conducted in our country, it is possible to see similar results in terms of depression and anxiety levels (11,23,24). In a study conducted in our country, female gender, chronic and psychiatric disease history were listed as the causes of increased anxiety (11). In our study group, there was no significant difference between two anxiety assessments at different times. More detailed data for the analysis of the causes are needed.

It has been seen that one of the important reasons for the increase in hopelessness levels in the COVID-19 pandemic is the fear of contagion (19). In our study, the hopelessness parameter was evaluated with the BHS. In the scale where the maximum score was 20, it was seen that the median score was 2 (range: 0-10 and 0-11, respectively) in both assessments. This low score result might be caused by the fact that our focus group did not have direct contact with the disease or other members of the community during lockdown, and had the opportunity to be isolated at home.

Stress occurs when there is an imbalance between the expectations of the social environment and the person's perception. Perceived stress is a subjective assessment tool that defines the level of stress in one's life. It allows to evaluate the person's sense of insecurity and the burden he/she feels (9). Female gender and physical activity restrictions are defined as the most common stressors. In our study, it was observed that there was a significant difference between the first and last PSS scores. This finding is consistent with current reports. It may be attributed to the restriction of movement, which was added to the feeling of uncertainty in the first evaluation, during the period when various lockdown measures were implemented. The final evaluation which belongs to a period in when the vaccination started and returning to normal life came to the fore.

Conclusion

When results of the subgroups were examined, it was seen that the PSS scores of high school graduate caregivers in the acute phase were higher than those of primary school graduate caregivers. In the chronic phase this outcome was reversed. Since the difference between the results was not statistically significant, it was not expressed in detail. However, this piece of outcome may gain statistical significance in further studies by using different scales and by evaluating a larger research group.

The fact of the pandemic, which will be remembered as the most important historical event of the 21st century, has created effects on the mental health of people worldwide that deserve to be examined. We see that the results of our study with mothers of children diagnosed with CP are significant. We think that it would be appropriate to support it with new studies to illuminate the areas where this study is limited.

Acknowledgment

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Ethics

Ethics Committee Approval: This study was approved by ethical committee with approval date and number as follows: 02/11/2021-2021/15/551.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Evaluation of Knowledge, Practices, and Attitudes Towards Coronavirus in Individuals Aged 20-64 Years

20-64 Yaş Arası Bireylerde Koronavirüs Hakkında Bilgi, Davranış ve Tutumunun Değerlendirilmesi

Beray Gelmez Taş[1], Hatice Rümeysa Selvi[2], Güzin Zeren Öztürk[1], Seçil Günher Arıca[2], Memet Taşkın Eğici[3]

[1]*University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Family Medicine, İstanbul, Turkey*

[3]*University of Health Sciences Turkey, İstanbul Haydarpaşa Numune Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey*

ABSTRACT

Background: This study was conducted to evaluate the knowledge, attitudes and practices of individuals aged 20-64 about Coronavirus disease-2019 (COVID-19).

Materials and Methods: In this study, an online questionnaire was applied to individuals between the ages of 20-64 registered at the Training Family Health Centre of the Okmeydanı Health Practices and Research Centre between 4-8 May 2020 through a phone application. The number of individuals between the ages of 20-64 years in these centres was 12.500, and the survey was sent to every person who owned a phone. One thousand one hundred thirty-eight surveys were included in the study. The confidence interval of our study was 1.96. The online questionnaire form consists of two parts: The first part includes the information form that assesses the socio-demographic data and the practice of personal protection and precautions, and the second part includes questions about knowledge, attitudes, and practices towards COVID-19.

Results: One thousand one hundred thirty-eight individuals participated in this study. The average age of the participants was 37.79 [standard deviation (SD): 9.68, minimum: 20, maximum: 64]. The average COVID-19 knowledge score was 10.26 (SD: 1.44, range 0-12). This value shows that in general, the participants correctly answered a proportion of 85.5% (10.26/12*100). Based on the multiple linear regression analysis, the female gender (compared to men β:-0.268, p=0.030), individuals with high school or higher education (compared to lower than high school, β: 0.479, p=0.008) and white-collar workers (compared to retired/not working β: -0.141, p=0.010), and those with an income of 4500 TL and higher (compared to 2.300 and lower β: 0.143, p=0.039) had statistically significantly high knowledge scores

Conclusion: Generally, the participants had a high level of knowledge of COVID-19. In particular, women, those with high educational levels, members of a white-collar profession group and those with high-income levels were more knowledgeable.

Keywords: COVID-19, knowledge, attitude

ÖZ

Amaç: Bu çalışma, 20-64 yaş arasındaki bireylerin Koronavirüs hastalığı-2019 (COVID-19) ile ilgili bilgi, tutum ve uygulamalarını değerlendirmek amacıyla yapılmıştır.

Gereç ve Yöntemler: Çalışma 4-8 Mayıs 2020 tarihleri arasında Okmeydanı Sağlık Uygulama Araştırma Merkezi Aile Hekimliği Kliniği'ne bağlı Eğitim Aile Sağlığı Merkezi'ne bağlı nüfustan 20-64 yaş arası bireylere telefon uygulaması üzerinden Google anket uygulanmıştır. Birey sayısı 12,500 olup; telefonu olan her bireye anket gönderilmiştir. Bün yüz otuz sekiz anket çalışmaya alınmıştır. Çalışmamızın güven aralığı 1,96'dır. Olgu rapor formumuz iki bölümden oluşmaktadır; İlk bölüm sosyo-demografik veriler ile kişisel korunma ve tedbirleri uygulama durumlarının değerlendirildiği bilgi formunu; ikinci bölüm ise COVID-19 ile ilgili bilgi, tutum ve davranış değerlendirme anketi sorularından oluşmaktadır.

Address for Correspondence: Beray Gelmez Taş, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey

Phone: +90 505 315 02 24 E-mail: drberaygelmez@hotmail.com **ORCID ID:** orcid.org/0000-0002-7126-0024

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ÖZ

Bulgular: Çalışmanın örneklemini 1,138 katılımcı oluşturmaktadır. Katılımcıların genel yaş ortalaması 37,79 [standart sapma (SS): 9,68, minimum: 20, maksimum: 64], %64,6'sı (n=735) kadın idi. ortalama COVID-19 bilgi skoru 10,26'dır (SS: 1,44, aralık 0-12). Bu değer genel olarak katılımcıların testi %85,5 (10,26/12*100) oranında doğru cevapladıklarını göstermektedir. Çoklu doğrusal regresyon analizine göre; kadın cinsiyetin (erkeklere göre β:-0,268, p=0,030); lise ve üstü eğitimli bireyler (lise ve altına göre, β: 0,479, p=0,008); beyaz yakalı çalışanlar (emekli/çalışmıyor göre β:-0,141, p=0,010); gelir durumu 4500 TL ve üstü olanlar (2300 TL ve altına göre β: 0,143, p=0,039) yüksek bilgi skorlarına sahip olup; istatistiksel olarak anlamlı idi.

Sonuç: Genel olarak, araştırmamıza katılanlar COVID-19 hakkındaki bilgi düzeyi yüksek olduğu görüldü. Özellikle kadınlar, eğitim seviyesi yüksek, beyaz yakalı meslek gruplarına mensup olanlar ile gelir seviyesi yüksek olanlar daha bilgili idi.

Anahtar Kelimeler: COVID-19, bilgi, tutum

Introduction

Coronavirus was first detected in 1965 by Tyrrell and Bynoe in a patient with a cold. It was then found that the hepatitis virus in mice and the gastroenteritis virus in pigs had the same morphology (1). Coronavirus has caused two epidemics in the last two decades: Severe acute respiratory syndrome and Middle East respiratory syndrome (2,3).

A series of new virus cases that caused respiratory infections were observed in humans after visiting the wild animal market in December 2019 in China (4). A new coronavirus was detected on January 7, 2020, and the disease it causes was named Coronavirus disease-2019 (COVID-19). The World Health Organization (WHO) declared the COVID-19 pandemic on March 11, 2020. (5). The first COVID-19 case in Turkey was detected on March 10, 2020. (6).

Currently, there is no treatment proven to be effective against COVID-19 infections (7). This situation has led to the prioritization of efforts in preventing transmission. COVID-19 infection is transmitted to humans by contact and droplets (8). It is predicted that the contagion begins 1-2 days before the patient's symptoms begin and ends with their disappearance (5). The transmission rate has varied between 1-5% in the studies performed (9). In our country, many precautions have been taken to prevent transmission and one of these is the curfew in place for individuals 20 years and younger and those 65 years and older (10,11).

The COVID-19 knowledge, attitudes and the behavior of individuals aged 20-64 who have outside contact are important for managing the relationship between home and society.

In our study, it was aimed to evaluate the knowledge, attitudes and practices of individuals aged 20-64 about COVID-19 and the factors affecting them.

Material and Methods

In this study, an online questionnaire was applied to individuals between the ages of 20-64 registered at the Training Family Health Centre (TRFHC) of the Okmeydanı Health Practices and Research Centre (Okmeydanı HPRC) between 4-8 May 2020 through a phone application. An online survey was applied to reduce contact during the pandemic. A voluntary consent form was added to the questionnaire and those who were approved were included in the study. The number of individuals between the ages of 20-64 years in the TRFHC of the Okmeydanı HPRC was 12.500, and the survey was sent to every person who owned a phone. One thousand one hundred thirty-eight surveys were included in the study. The confidence interval (CI) of our study was 1.96.

Approval for the study was obtained from University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital HPRC Ethics Committee with the decision numbered 129 on 28.04.2020.

The online questionnaire form consists of two parts: The first part includes the information form that assesses the socio-demographic data and the practice of personal protection and precautions, and the second part includes questions about knowledge, practices and attitudes regarding COVID-19 contained in the survey created by Zhong et al. (12). The permission for use of the survey was received from Yi Li et al. MD, PhD who working Wuhan Mental Health Center on 11.04.2020 by e-mail. Subsequently, we translated it to Turkish.

The survey developed by Zhong et al. (12) consists of 16 questions in total. The first part contains 12 statements, 4 of which question (K1-K4) the clinical symptoms, 3 (K5-K7) question the transmission modes and 5 (K8-K12) inquire about precaution and control. Except for the statements K6 and K9, the other statements of the survey contain accurate information. Scoring is based on knowing whether the statement is correct, and each correct answer score 1 point. If the answer is incorrect or unknown, the score is 0. It was accepted that the total knowledge score was minimum 0, maximum 12, and as the score increased, the knowledge level increased. The Cronbach's alpha value of the information part of the questionnaire comprising 12 questions was calculated as 0.76. Since this value was

higher than 0.5 recommended by Cronbach and Helmstater and 0.7 recommended by Bowling and Ebrahim (13,14), it can be concluded that the survey prepared is reliable.

In the continuation of the questionnaire in our study, one question was added to the questions in both the attitude and practices questions of Zhong et al.'s (12) questionnaire (A3 and P3). Thus, the attitudes related to COVID-19 were evaluated by 3 questions (A1, A2, A3) and the practices were evaluated by 3 questions (P1, P2, P3).

Statistical Analysis

The data were categorized categorically and individually. The numerical data were presented as mean and standard deviation and the categorical data as median and percentages. The t-tests were used to compare the numerical data and the chi-square tests were used to compare the categorical data. Various attitudes and practices were defined by the frequency of correct knowledge answers. The multivariate linear regression analysis, which uses all demographic variables as independent variables and the knowledge score as the result variable, was carried out to identify the factors related to knowledge. Similarly, binary logistic regression analyses were used to identify the factors associated with attitudes and practices. The factors were selected by a backward stepwise method. The non-standardized regression coefficients (β), the odds ratios (OR) and the 95% CIs were used to assess the relationships between the variables and knowledge, attitudes, and practices. P-value was determined as 0.05 and the SPSS 21 software was used for statistical analysis.

Results

One thousand one hundred thirty-eight individuals participated in this study. The mean age of the participants was 37.79 [standard deviation (SD): 9.68, min: 20, max: 64]; 64.6% (n=735) were women, 93.4% (n=1063) had educational levels of high school and higher, 64.0% (n=728) were married, 72.0% (n=819) were white-collar workers and 56.8% (n=646) had an income of 4500 TL and higher.

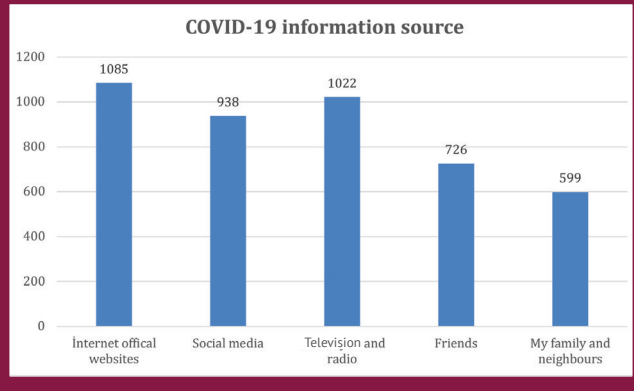
Reviewing the distribution of answers given to the question "Do you believe that you have sufficient knowledge about COVID-19?" showed that 63.6% (n=923) stated that they had sufficient knowledge, 2.6% (n=30) stated that they had insufficient knowledge and 33.7% (n=384) stated that they had partial knowledge about COVID-19. When we looked at the distribution of multiple-choice answers to the question "What is/are your information resource or resources about COVID-19?", it was identified that 24.8% (n=1.085) used official web sites (Ministry of Health of Turkey, WHO, Centres for Disease Control, etc.) as their information source (Graph 1). These were followed by visual and social media.

32.5% (n=370) answered yes to the question, "Do you know anyone who is suffering/ has suffered from COVID-19?" Of the participants, 23.8% (n=271) stated that they wanted to have a COVID-19 test to the question, "Did you want to have a COVID-19 test because you were worried despite not having any complaints?"

Assessment of Personal Protection and Precautionary Practices

The participants were asked about their practices of personal protection and precautions in compared to the time before COVID-19. It was identified that the practice of "frequent ventilation of the environment" increased in 81.1% (n=923), decreased in 0.6% (n=7), and had not changed in %28.3% (n=208). The practice of "cleaning surfaces you frequently use with water and detergent frequently" increased in 77.1% (n=877), decreased in 0.8% (n=9), and had not changed in 21.1% (n=252). It was identified that the practice of "sharing personal belongings such as towels" increased in 23.2% (n=264), decreased in 45.2% (n=514), and had not changed in 31.6% (n=360).

The practice of "washing clothes at high temperatures" increased in 51.1% (n=581), decreased in 2.2% (n=25), and had not changed in 46.7% (n=532). The practice of "refraining from close contacts such as shaking hands and hugging" increased in 62.6% (n=712), decreased in 35.3% (n=402) and had not changed in 2.1% (n=24). It was identified that the practice of "washing hands with water and soap frequently for at least 20 seconds by rubbing" increased in 89.8% (n=1022), decreased in 1.7% (n=19), and had not changed in 8.5% (n=97). It was determined that the practice of "cleaning of products bought at the shops at home" increased in 83.0% (n=944), decreased in 2.7% (n=31), and had not changed in 14.3% (n=163). Accordingly, the personal protection method



Graph 1. The distribution of participants' COVID-19 information sources

COVID-19: Coronavirus disease-2019

that increased the most was "washing hands frequently with soap and water for at least 20 seconds by rubbing".

Knowledge, Attitude and Practices Towards COVID-19 Assessment Questionnaire

The answers and the questions of the knowledge survey have been presented in Table 1 and the average COVID-19 knowledge score was 10.26 (SD: 1.44, range 0-12). This value shows that in general, the participants correctly answered a proportion of 85.5% (10.26/12*100). The knowledge statement known most accurately was, "People who have contact with someone infected with the COVID-19 virus

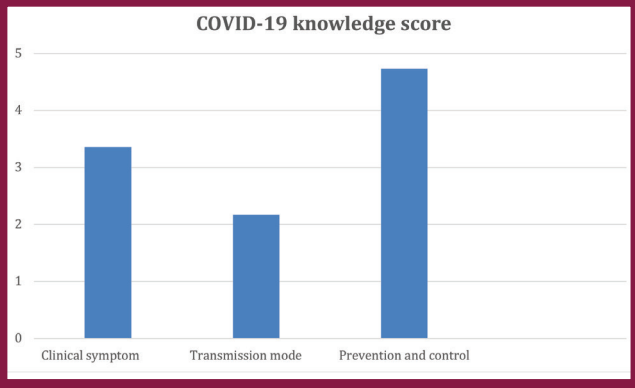
Table 1. COVID-19 knowledge, attitude and practice assessment questionnaire

Questions		N	%
K1: The main clinical symptoms of COVID-19 are fever, fatigue, dry cough, and myalgia.	True	1.102	96.8
	False	17	1.5
	I don't know	19	1.7
	Total	1.138	100
K2: Unlike the common cold, stuffy nose, runny nose, and sneezing are less common in persons infected with the COVID-19 virus.	True	710	62.4
	False	214	18.8
	I don't know	214	18.8
	Total	1.138	100
K3: There currently is no effective cure for COVID-19, but early symptomatic and supportive treatment can help most patients recover from the infection.	True	1.075	94.5
	False	24	2.1
	I don't know	39	3.4
	Total	1.138	100
K4: Not all persons with COVID-19 will develop severe infections. Only those, who are elderly, have chronic illnesses and are obese are more likely to become severe cases.	True	927	81.5
	False	156	13.7
	I don't know	55	4.8
	Total	1.138	100
K5: Eating or contacting wild animals would result in infection by the COVID-19 virus.	True	385	33.8
	False	417	36.6
	I don't know	336	29.5
	Total	1.138	100
K6: Persons with COVID-19 cannot infect the virus to others when a fever is not present.	True	23	2
	False	993	87.3
	I don't know	122	10.7
	Total	1.138	100
K7: The COVID-19 virus spreads via respiratory droplets of infected individuals.	True	1.058	93
	False	29	2.5
	I don't know	51	4.5
	Total	1.138	100
K8: All individuals can wear medical masks to prevent the infection by the COVID-19 virus.	True	949	83.4
	False	128	11.2
	I don't know	61	5.4
	Total	1.138	100
K9: It is not necessary for children and young adults to take measures to prevent the infection by the COVID-19 virus.	True	48	4.2
	False	1.061	93.2
	I don't know	29	2.5
	Total	1.138	100
K10: To prevent the infection by COVID-19, individuals should avoid going to crowded places such as train stations and avoid public transportation.	True	1.100	96.7
	False	23	2
	I don't know	15	1.3
	Total	1.138	100
K11: Isolation and treatment of people who are infected with the COVID-19 virus are effective ways to reduce the spread of the virus.	True	1.108	97.4
	False	15	1.3
	I don't know	15	1.3
	Total	1.138	100
K12: People who have contact with someone infected with the COVID-19 virus should be immediately isolated in a proper place. In general, the observation period is 14 days.	True	1.117	98.2
	False	12	1.1
	I don't know	9	0.8
	Total	1.138	100
A1. Do you agree that COVID-19 will finally be successfully controlled?	Agree	678	59.6
	Disagree	137	12
	I don't know	323	28.4
	Total	1.138	100
A2. Do you have confidence that Turkey can win the battle against the COVID-19 virus?	Yes	944	83
	No	194	17
	Total	1.138	100
A3: Do you believe that individuals are complying with the prohibitions/ precautions implemented for COVID-19?	Yes	338	29.7
	No	800	70.3
	Total	1.138	100
P1. In recent days, have you gone to any crowded place?	Yes	168	14.8
	No	970	85.2
	Total	1.138	100
P2. In recent days, have you worn a mask when leaving home?	Yes	1.089	95.7
	No	49	4.3
	Total	1.138	100
P3: Do the individuals in your family comply with the prohibitions?	Yes	1.030	90.5
	No	10	0.9
	Partially	98	8.6
	Total	1.138	100
COVID-19: Coronavirus disease-2019			

should be immediately isolated in a proper location. In general, the observation period is 14 days." with 98.2%. The least known was "Eating or contact with wild animals would result in the infection by COVID-19", with 33.8%.

No statistically significant relationship was determined between the COVID-19 knowledge score applied to the participants and age (r=-0.019 p=0.528).

When the relationship between the demographic variables and the COVID-19 knowledge score was examined, a statistically significant difference was found between gender (p=0.027), educational status (<0.001), professional status (<0.001) and the income status (<0.001) (Table 2).



Graph 2. The distribution of COVID-19 knowledge score subscale score averages

COVID-19: Coronavirus disease-2019

Based on the multiple linear regression analysis, the female gender (compared to men β:-0.268, p=0.030), individuals with high school or higher education (compared to lower than high school, β: 0.479, p=0.008) and white-collar workers (compared to retired/not working β: -0.141, p=0.010) and those with income an income of 4500 TL and higher (compared to 2300 and lower β: 0.143, p=0.039) had statistically significantly high knowledge scores (Table 3).

The subscale scores have been presented in Graph 2. Accordingly, the subscale that was known most was prevention and control, and the least known was the transmission mode.

The assessment of the subscales of the knowledge score and demographic data did not show a statistically significant relationship between clinical symptoms, transmission mode, control and prevention scores, and age (r=-0.017 p=0.561; r=-0.002 p=0.942; r=-0.003, respectively; p=0.917). The transmission mode scores showed statistically significant differences between females and males. It was observed that the transmission mode scores were higher in women than in men (Z=-3.308, p=0.001). There was no relationship between the clinical symptoms, prevention, the control subscales, and gender.

It was observed that the clinical symptom and the transmission mode scores were higher in white-collar participants than in the other profession groups (Z=35.702, p<0.001; Z=21.403, p<0.001, respectively). It was identified that the prevention and control scores were higher in participants who were retired or not working compared to the other profession groups (Z=8.865, p=0.031).

Table 2. The demographic characteristics of the participants and the analysis of the COVID-19 knowledge score based on demographic variables (n=1138)

Demographic variables		Number of participants (%)	Knowledge score (mean ± standard deviation)	Z/KV	p
Gender	Female Male	735 (64.6) 403 (35.4)	10.3±1.3 10.1±1.5	-2.207	**0.027**
Age group (years)	20-29 30-49 50-64	244 (21.4) 733 (64.4) 161 (14.1)	10.3±1.3 10.2±1.4 10.2±1.4	0.307	0.858
Education level	Below high school High school and higher	75 (6.6) 1.063 (93.4)	9.6±1.9 10.3±1.3	-3.507	**<0.001**
Marital status	Married Single Divorced/widowed	728 (64.0) 333 (29.3) 77 (6.8)	10.3±1.4 10.1±15.5 10.1±1.3	2.934	0.231
Professional status	White collar Blue collar Retired/not working student	819 (72.0) 94 (8.3) 165 (14.5) 60 (5.3)	10.4±1.3 9.6±2.0 10.0±1.3 9.8±1.6	38.182	**<0.001**
Income level	<2.300 TL 2.300-4.500 TL >4.500 TL	181 (15.9) 311 (27.3) 646 (56.8)	9.9±1.5 10.1±1.4 10.4±1.3	30.740	**<0.001**

COVID-19: Coronavirus disease-2019

Table 3. The multiple linear regression analysis of demographic variables related to the COVID-19 knowledge score

Variables	β	Standard error	t	p
Gender (female-male)	-0.268	0.89	-3.011	**0.030**
Educational level	0.479	0.179	2.670	**0.008**
Profession	-0.141	0.54	-2.595	**0.010**
Income level	0.143	0.69	2.071	**0.039**
COVID-19: Coronavirus disease-2019				

No statistically significant difference was identified between the prevention and control subscale scores and the income levels. It was observed that the clinical symptoms and the transmission mode scores were higher in participants with an income higher than 4500 TL compared to the other income level groups (Z=34.969, p<0.001; Z=7.687, p=0.021, respectively).

When the attitude questions were reviewed, it was identified that 59.6% of the participants had stated that they agreed that COVID-19 would finally be successfully controlled, 12% stated that they disagreed, and 28.4% stated that they did not know. It was identified that 83% of participants believed that Turkey could win the battle against COVID-19 and 17% did not. It was observed that 29.9% of the participants believed that individuals complied with the prohibitions/precautions implemented for COVID-19 and 70.1% did not.

It was determined that 14.7% of the participants had gone to a crowded place and 85.3% had not. It was determined that 95.7% of the participants used masks when leaving home and 4.3% did not. It was determined that 90.5% of the participants believed that individuals in the family complied with the prohibitions/precautions, 0.9% did not comply and 4.3% partially complied.

In the review of the results of the multiple logistic regression analysis, a significant relationship was determined for the answer "agree" given to the question "Do you agree that COVID-19 will finally be successfully controlled?" between those retired/not working (compared to students OR: 1.59, p=0.006), and those with an educational level higher than high school (compared to lower than high school OR:1.59, p=0.006).

The female gender (compared to male OR: 0.59, p<0.001) and being a white-collar worker (compared to blue-collar OR: 0.41, p=0.021) were found to be significantly associated with the answer "I don't know" given to the question "Do you agree that COVID-19 will finally be successfully controlled?"

Being married (compared to single OR: 1.59, p=0.006) and (compared to others OR: 1.96, p=0.017), having an educational level higher than high school (compared to lower than high school OR: 2.45, p=0.032) were found to be significantly associated with the answer "yes" given to the question "Do you have confidence that Turkey can win the battle against the COVID-19 virus?"

The male gender (compared to female OR: 0.63, p=0.001), white-collar workers (compared to blue collars OR: 0.55, p=0.007), and blue-collar workers (compared to students OR: 2.12, p=0.038) were found to be significantly associated with the answer "yes" given to the question "Do you believe individuals follow the prohibitions/precautions for COVID-19?" A significant relationship was determined between being married (compared to single OR: 0.58, p=0.003) and (compared to others OR: 0.47, p=0.014) having an income level lower than 2300 TL (compared to higher than 4.500 OR: 0.55, p=0.029) and going to a crowded place.

Among the demographic variables, a statistically significant difference was only found between the participants' practice scores and the marital status.

Discussion

The way to facilitate compliance with transmission prevention efforts is to increase the knowledge level and awareness of the society. In this study, 63.6% (n=923) of the participants believed that they had sufficient knowledge about COVID-19. Similar to the studies in the literature, 95.3% of the participants preferred the internet as the source of information (15,16,17,18). The internet has brought a significant change to traditional forms of communication and has irreversibly diversified the dimensions of communication (19).

Today, when internet access is so widespread, it is inevitable that it will be used as an information source. However, it should not be forgotten that correct information can only be obtained from the proper source. For this reason, every country should create official websites and health-themed television channels in their native language to spread information and answer questions through an online response system if necessary.

One out of every four individuals among the participants still wanted to have a test despite not having any complaints. This may be due to the presence of asymptomatic individuals with a COVID-19 infection and their contagiousness (20).

The WHO also emphasizes meticulous attention to personal hygiene rules such as hand washing to prevent transmission through contact (21). Similar to other studies, the participants reported an increase in practicing protective measures such as social distancing, hand hygiene, cleaning of surfaces, ventilation of the environment and cleaning products coming from a store (16,17,22,23). The highest increase was in the handwashing habit, and this is due to this practice being the fundamental preventive practice advised by many health authorities from the first instant.

The score measuring the knowledge sufficiency of the knowledge attitude practice questionnaire applied was 10.26, and this shows that participants answered correctly at a rate of 85.5%. Generally, it was identified that most of the participants of our survey knew about the clinical condition, mode of transmission and the preventive measures. Similar to our studies, in studies investigating the COVID-19 knowledge level, the correct knowledge level was 90% in the study conducted by Zhong et al. (12) and 71.2% in a study carried out in Egypt (17).

In the literature, there are studies showing that increasing the knowledge of individuals during pandemics affects the attitude towards the pandemic and compliance with protective precautions (24,25). For this reason, activities that would inform the public and raise awareness should be included in efforts to prevent pandemics.

Similar to another study, the knowledge score in our study increased statistically significantly in women, in those with a high income and educational level and in white-collar workers (12). The concepts of having a high income and educational level and being a white-collar worker are inter-related. Furthermore, some studies show that there is a positive relationship between education and the knowledge levels (17,23,26).

In our study, the statement "People who have contact with someone infected with the COVID-19 virus should be immediately isolated in a proper place for 14 days" was answered correctly at the highest rate by the participants (98.2%). The rate of knowledge of this statement was 97.3% in the study by Zhong et al. (12) and 95.8% in the study by Abdelhafiz et al. (17). In our study, the statement "Eating or contacting wild animals would result in the infection by the COVID-19 virus" had the lowest rate (33.8%) of correct answers. The rate of knowing this statement was 91.4% in a study organized in China. In our country, eating wild animals is not preferred due to our religion and cultural structure. Therefore, this aspect is unknown.

According to the subscale scores, prevention and control were the most known, and the transmission mode was the least known. While there was no difference in gender in the other subscales, it was determined that the knowledge status of women about transmission modes was higher than men. This may be due to women paying more attention, because they have several responsibilities in cleaning, hygiene, food, and care of children. The clinical symptoms and transmission modes being known to a higher extent among white-collar workers explains its relationship with high-income levels.

In our study, 40.4% of the participants believed that COVID-19 would unsuccessfully be controlled. This may be due to the fact that 70.3% of the participants had stated that it is believed that individuals do not comply with protective measures. According to a study performed in China, the rate of believing that prohibitions are being followed was lower (12). However, in our study, it was determined that 83% of the participants believed that Turkey could win the battle against COVID-19. In Turkey, the MoH of Turkey has pursued a transparent policy and access to information, and follow-up of the number of cases has been enabled through the official web site and applications. These efforts have also increased the public confidence in the health infrastructure and caused the majority to believe that Turkey will win this battle.

When we looked at the answers given to the practice questions, most of the individuals stated that they and the people living near them followed the rules. This rate is higher than that of a study in India (22). We believe that this practice compliance is due to the knowledge levels of the participants of our study being higher than that in the India study. Knowledge affects attitudes and practices and increases the compliance.

Study Limitations

The limitations of our study comprise having been conducted in a single center and the scarcity of similar studies.

Conclusion

Generally, it was observed that the COVID-19 knowledge levels of the participants in our study were high. In particular, women, those with high educational levels, members of the white-collar profession group and those with high-income levels were more knowledgeable. Official web sites on the internet were used most as information sources. Thus, correct information was obtained from the proper source. In Turkey, the MoH pursued a transparent policy since the first case, and information and daily sharing of new case numbers provided on the official web site may play a role in the high rate of following the official web sites.

Participants showed positive attitudes and practices towards the use of protective measures, which are essential to prevent the transmission of the disease. We think that this result is due to high knowledge levels affecting attitudes and practices.

Ethics

Ethics Committee Approval: Approval for the study was obtained from University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital HPRC Ethics Committee with the decision numbered 129 on 28.04.2020.

Informed Consent: A voluntary consent form was added to the questionnaire and those who were approved were included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.G.T., H.R.S., G.Z.Ö., S.G.A., M.T.E., Concept: B.G.T., H.R.S., G.Z.Ö., Ş.G.A., M.T.E., Design: B.G.T., H.R.S., G.Z.Ö., S.G.A., M.T.E., Data Collection or Processing: B.G.T., Analysis or Interpretation: B.G.T., H.R.S., G.Z.Ö., Literature Search: B.G.T., H.R.S., G.Z.Ö., S.G.A., M.T.E., Writing: B.G.T., H.R.S., G.Z.Ö.

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Evaluation COVID-19 and Professional Anxiety of Medical Faculty Students

Tıp Fakültesi Öğrencilerinin COVID-19 Anksiyete Düzeyi ve Mesleki Kaygı Durumlarının Değerlendirilmesi

Yeşim Uslu[1], Güven Bektemür[2], Güzin Zeren Öztürk[1], Memet Taşkın Egici[3], Erdoğan Çetinkaya[4]

[1]*University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey*

[2]*University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Department of Public Health, İstanbul, Turkey*

[3]*University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey*

[4]*University of Health Sciences Turkey, Hamidiye Faculty of Medicine, Department of Pulmonology, İstanbul, Turkey*

ABSTRACT

Background: In this study, we evaluated the Coronavirus disease-2019 (COVID-19) anxiety levels and occupational anxiety levels of medical faculty students (MFS) during the COVID-19 pandemic.

Materials and Methods: The population of this descriptive and single-center study consisted of MFS in January 2021. After the literature review, the form prepared by us and the coronavirus anxiety scale (CAS) were sent to all MFS via the internet. Before answering the form questions, detailed information about the study was given and an informed consent form was presented. Only students who marked the "I approve" option on the informed consent form participated in the study. In the form, contains questions about their socio-demographic data, career choice and educational status, changes in the COVID-19 period and their results. At the end of the form, the CAS was applied.

Results: Two hundred-fifty one MFS participated in our study and the mean age was 21.14±2.16 (minimum: 18, maximum: 35). 51.8% (n=130) of MFS were male and 8.8% (n=22) had a chronic disease. The rate of smokers was 19.1% (n=48) and 78.1% (n=196) of MFS lived with their families.

The mean score of the participants on the CAS was determined as 1.06±2.24 (minimum: 0, maximum: 15). CAS scores was found to be statistically significantly higher in those participants aged 23 and over, women, those has chronic diseases, those recovered from COVID-19 without any medication, those who have fear of infected with COVID-19, those who change their specialization preferences during the pandemic, those who think that using PPE is insufficient to protect against COVID-19, those who thought to interrupt or drop out their medical education due to the COVID-19 pandemic (p=0.002, p<0.001, p=0.044, p=0.033, p<0.001, p<0.001, p=0.034, p=0.003, respectively).

Conclusion: CAS increased with age, female gender, having a chronic disease, fear of infecting with COVID-19 and not thinking that using PPE is sufficient to protect against COVID-19.

Keywords: COVID-19, anxiety, education

Address for Correspondence: Yeşim Uslu, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Family Medicine, İstanbul, Turkey

Phone: +90 545 267 01 47 E-mail: yesimuslu94@gmail.com **ORCID ID:** orcid.org/0000-0001-9604-3555

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ÖZ

Amaç: Biz bu çalışmamızda Koronavirüs hastalığı-2019 (COVID-19) pandemisi sürecinde tıp fakültesi öğrencilerinin (TFÖ) COVID-19 anksiyete düzeylerini ve mesleki kaygı durumlarını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu tanımlayıcı ve tek merkezli çalışmanın popülasyonu Ocak 2021'deki TFÖ'den oluşmaktadır. Literatür taraması sonrası tarafımızda hazırlanan sorgulama formu ve koronavirüs anksiyete ölçeği (KAÖ) internet üzerinden tüm TFÖ'ye iletilmiştir. Form sorularından önce çalışma hakkında detaylı bilgi verildi ve bilgilendirilmiş onam formu sunulmuştur. Çalışmaya sadece bilgilendirilmiş onam formunda "Onaylıyorum" seçeneğini işaretleyen öğrenciler katılmıştır. Anket formunda sosyo-demografik verileri, meslek seçimi ve eğitim durumları, COVID-19 dönemindeki değişiklikler ve sonuçları ile ilgili sorular yer almaktadır. Formun sonunda KAÖ uygulanmıştır.

Bulgular: Çalışmamıza 251 TFÖ katıldı ve yaş ortalamaları 21,14±2,16 (minimum: 18 maksimum: 35) idi. TFÖ'nün %51,8'i (n=130) erkekti ve %8,8'i (n=22) kronik bir hastalığa sahipti. Sigara içenlerin oranı %19,1 (n=48) idi ve %78,1'i (n=196) ailesiyle birlikte yaşıyordu. Katılımcıların KAÖ puan ortalamaları 1,06±2,24 (minimum: 0 maksimum: 15) olarak saptandı. KAÖ puanları 23 yaş ve üstü kişilerde, kadınlarda, kronik hastalığı olanlarda, COVID-19 ile enfekte olanlardan hastalığı tedavisiz geçirenlerde, COVID-19'dan korktuğunu belirtenlerde, pandemiden sonra tıpta uzmanlık bölümü tercihleri değişmiş olanlarda, KKE'nin COVID-19'dan korunmada yetersiz olduğunu düşünenlerde ve COVID-19 pandemisi nedeniyle tıp eğitimini bırakmayı ya da dondurmayı düşünenlerde istatistiksel olarak anlamlı şekilde daha yüksek saptanmıştır (sırasıyla; p=0,002, p<0,001, p=0,044, p=0,033, p<0,001, p<0,001, p=0,034, p=0,003).

Sonuç: KAÖ puanları kadın cinsiyet, kronik bir hastalığa sahip olma, COVID-19 ile enfekte olmaktan korkma, KKE kullanmanın COVID-19'dan korunmak için yeterli olmadığını düşünme durumlarında ve yaş ile artıyordu.

Anahtar Kelimeler: COVID-19, anksiyete, eğitim

Introduction

The occupation can be defined as the activities that people do both to earn a living and to realize themselves, and for this reason, the choice of profession is one of the biggest milestones in people's lives (1,2). While it has been determined by studies that students have various anxieties before starting to university, after their knowledge about the profession increases during university education, their anxiety continues by differentiating. Medical faculty students (MFS) experience higher rates of psychological problems compared to the other faculty students and the general population, due to the extensive content, performance pressure, self-pressure for good grades, keeping up to date with knowledge, fear of making mistakes and medical school workload (3,4,5).

Although medicine is among the most dangerous professions, it is also one of the most demanded and respected professions. According to a study conducted in Turkey in 2020, medicine is one of the two professions that are in the top 10 professions that are both desirable and undesirable. This may be caused by factors such as the difficulty of working conditions, work and shift systems, workplace stress and high probability of occupational accidents (6).

The Coronavirus disease-2019 (COVID-19) has affected the whole world since December 2019 and has caused various problems such as social isolation, disruption of education and economic difficulties. Education method changes due to the pandemic have caused difficulties for students. MFS have also witnessed the difficulties experienced by healthcare professionals due to the pandemic. An increase in anxiety can be expected in this group, who faced the problems they may experience in the future. As a matter of fact, some studies conducted during the pandemic have shown that MFS have high levels of anxiety (7,8).

In this study, we aimed to evaluate the COVID-19 anxiety levels and occupational anxiety levels of MFS during the COVID-19 pandemic.

Material and Methods

Study Population and Sample

The population of this descriptive and single-center study consisted of MFS in January 2021. Since our university was newly established, there are students up to the 5th grade.

In January 2021, the total number of MFS in University of Health Sciences Turkey is 730. The sample size was calculated as at least 252 MFS with a 95% confidence interval.

The protocol of this study was approved by the Ethics Committee of University of Health Sciences Turkey on 04/12/2020 (number: E-46418926-050.01.04).

Data Collection Tools

After the literature review, the form prepared by us and the questions consisting of the coronavirus anxiety scale (CAS) were sent to all medical school students via the internet. Before answering the form questions, detailed information about the study was given and an informed consent form

was presented. Only students who marked the "I approve" option on the informed consent form participated in the study. Participation in the study is completely voluntary.

In the form, contains questions about their socio-demographic data, career choice and educational status, changes in the COVID-19 period and their results. At the end of the form, the "CAS" was applied.

CAS

The "CAS" was used to measure the COVID-19 anxiety levels of the students. This scale was developed by Lee (9), and its Turkish validity study was conducted in 2020 by Evren et al. (10). It is made up of five items employing a 5-point Likert scale and participants are asked how often they have experienced the conditions found in the questions during the last 2 weeks. Scoring of the scale was "0" "not at all", "1" "rare, less than a day or two", "2" "several days", "3" "more than 7 days" and "4" "nearly every day over the last 2 weeks". The higher the score, the higher the anxiety level.

Statistical Analysis

IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, N.Y., USA) was used for the data analysis. Descriptive statistics for continuous variables were expressed as mean, standard deviation, minimum and maximum; categorical variables were expressed as number and percentage. The normality of the data set was confirmed by Kolmogorov-Smirnov test and it was determined that the measurements in the study were not distributed normally. Comparisons between groups were made using the Mann-Whitney U test for continuous variables. Spearman correlation analysis was used for the correlation relationship of continuous variables. Chi-square tests were used to compare categorical data. A p-value of <0.05 was considered statistically significant.

Results

Two hundred-fifty one MFS participated in our study and the mean age was 21.14±2.16 (minimum: 18, maximum: 35). 51.8% (n=130) of MFS were male and 8.8% (n=22) had a chronic disease. The rate of smokers was 19.1% (n=48) and the smokers had an average smoking history of 1.72±1.98 (minimum: 0.3, maximum: 8) packyears. 78.1% (n=196) of MFS lived with their families.

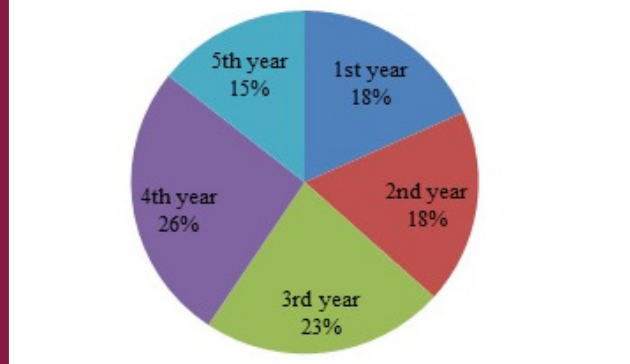
81.7% (n=205) MFS stated that they did not have COVID-19, 10.8% (n=27) had COVID-19 and recovered with outpatient treatment, 7.6% (n=19) stated that they had COVID-19 but recovered without any treatment. There were no MFS that treated hospital or intensive care.

As age increases, the rate of having COVID-19 increases (p=0.002). MFS with chronic disease were found to have a statistically significant higher incidence of COVID-19 (p=0.008), but no statistical difference was found between having COVID-19 and gender, smoking status (p=0.212, p=0.081, respectively).

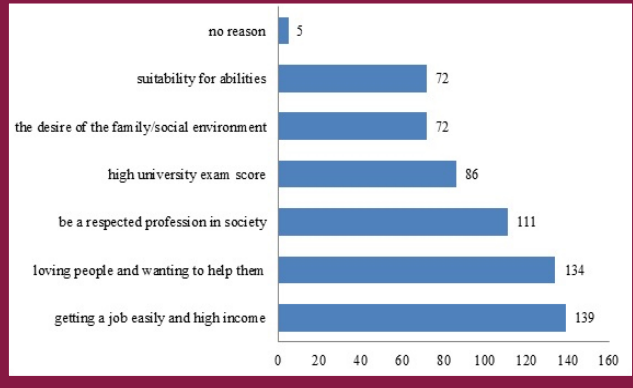
MFS' relatives had COVID-19, 76 (30.3%) of them stated that none of their relatives had COVID-19. Among those whose relatives had COVID-19, 111 participants (44.2%) stated that they recovered with outpatient treatment, 19 participants (7.6%) stated that recovered with inpatient treatment, 17 participants (6.8%) stated that recovered without any treatment, 10 participants (4%) stated that recovered with intensive care treatment and 18 (7.2%) participants stated that their relatives died due to COVID-19.

The distribution of MFS' academic years of the study is given in Graph 1. 228 students (90.8%) stated that they chose the medical faculty themselves. The reasons for choosing the medical faculty, was mostly getting job easily and high income at the rate of 55.4 (n=139) (Graph 2).

One hundred-seventy (67.7%) MFS stated that they had received training about the use of personal protective equipment (PPE). Most of MFS stated that the use of PPE was sufficient to prevent transmission and they felt safe (n=162; 64.5%); but 126 (50.2%) MFS thought that there



Graph 1. Distribution of participants' academic years of the study



Graph 2. Reasons for choosing the medical profession of the participating medical students

might be a problem in the supply of PPE. Those who received PPE training thought that the use of PPE was sufficient to prevent transmission and they felt safe, and thought that there might be no problem in the supply of PPE (p=0.04, p=0.012, respectively).

41.8% (n=105) of MFS stated that they were not sufficiently aware of the risks of being a physician before the COVID-19 pandemic. 80.1% (n=201) of MFS think that their medical education was disrupted during the pandemic.

When asked whether the pandemic had any effect on their preference for specialization in medicine, 85.7% (n=215) MFS stated that there was no change in their preference for specialization. Due to the effect of pandemic, while specialties with few or no shifts preferred by 23 students (9.2%), specialties not in contact with the patient preferred by 7 students (2.8%). However, 6 students (2.4%) tend to specialties dealing with COVID-19 in the frontlines.

The appreciation of healthcare professionals and the understanding of the importance of healthcare during the pandemic led to an increase in the professional motivation of 63.7% (n=160) of MFS. 84.5% (n=212) of MFS stated that they approve of physicians who resigned or retired during the pandemic period. The rate of MFS considering interruption or dropping out of medical education due to the pandemic was determined as 10.4% (n=26). The situation of considering of interruption or dropping out medical education is more often in those who did not increase their professional motivation during the pandemic, those who did not choose the medical profession themself, those who did not know the risks of the medical profession before the pandemic, those who thought that the use of PPE was insufficient for protection from COVID-19 and those who thought that there might be a problem in the supply of PPE. These situations are statistically significant (p<0.001, p<0.001, p=0.034, p=0.003, p=0.004, respectively).

46.2% (n=116) of the MFS stated that they had a fear of infected with COVID-19 because they were medical students. The relationship between the study data of people who have and do not have fear of infected with COVID-19 is given in Table 1. The mean age of individuals who were afraid of infected with COVID-19 was significantly higher (p=0.004). When we grouped the age, it was found that the 18-22 age group experienced less fear than the age group 23 and older (p=0.009). The fear of infected with COVID-19 was found to be statistically significantly more common in the following situations: Female gender, living with a person whom has a chronic disease, not having any relatives infected with COVID-19, having any relatives who got intensive care treatment because of COVID-19, thinking of medical education has been disrupted due to the pandemic, thinking that using PPE is insufficient to protect against COVID-19, changing specialization preferences due to the pandemic, considering interruption or dropping out medical education due to the pandemic (p=0.001, p=0.03, p=0.14, p=0.031, p=0.029, p=0.001, p=0.003, p=0.001, respectively). In the other hand, fear of infected with COVID-19 was found to be statistically significantly less frequent in cases of being in the first year of medical school, knowing the risks of the medical profession before the pandemic, trusting their institution to provide PPE (p=0.004, p=0.015, p=0.001, respectively).

The mean score of the participants on the CAS was determined as 1.06±2.24 (minimum: 0, maximum: 15). No correlation was found between age and CAS scores (p=0.343). The relationship between the CAS and the study data of the individuals is given in Table 2. CAS scores were found to be statistically significantly higher in those participants aged 23 and over, women, those has chronic diseases, those recovered from COVID-19 without any medication, those who have fear of infected with COVID-19, those who change their specialization preferences during the pandemic, those who think that using PPE is insufficient to protect against COVID-19, those who thought to interrupt or drop out their medical education due to the COVID-19 pandemic (p=0.002, p<0.001, p=0.044, p=0.033, p<0.001, p<0.001, p=0.034, p=0.003, respectively).

Discussion

During the pandemic period, healthcare workers are dealing with COVID-19 in the frontline. In this period, according to Amnesty International report dated March 5, 2021, more than 17,000 healthcare workers worldwide died due to COVID-19, and according to CDC data dated June 1, 2021, 1.635 healthcare workers in the United States alone (11,12). This situation may have caused medical school students to have fear and anxiety as it increased their awareness of occupational risks. In this study, it was aimed to investigate the fear and anxiety states of MFS and the factors affecting them.

46.2% (n=116) of the students participating in our study stated that they had a fear of infecting with COVID-19 because they were MFS. There are studies with various scales in the literature and in a study conducted with MFS in China in 2020, it was determined that 24.9% of the MFS were worried due to the COVID-19 pandemic (8). In a study conducted with MFS in Turkey, 59.9% of the students stated that they were worried about having COVID-19 (13).

Table 1. Relationship between study data of participants with and without fear of infecting with COVID-19

	Participants who have fear of infecting with COVID-19		Participants who have not fear of infecting with COVID-19		p
	N	%	N	%	
Age					
18-22	90	42.7	121	57.3	**0.009**
⩾23	26	65.0	14	35.0	
Gender					
Male	47	36.2	83	63.8	**0.001**
Female	69	57.0	52	43.0	
Having a chronic disease					
Yes	14	63.6	8	36.4	0.086
No	102	44.5	127	55.5	
Smoking					
Yes	22	45.8	26	54.2	0.953
No	94	46.3	109	53.7	
Living					
Alone	7	50.0	7	50.0	0.975
With friends	8	42.1	11	57.9	
With family	91	46.4	105	53.6	
In dormitory	10	45.5	12	54.5	
Living with a person whom has a chronic disease					
Yes	42	56.8	32	43.2	**0.030**
No	74	41.8	103	58.2	
Status of infected with COVID-19					
Yes	17	37.0	29	63.0	0.192
No	99	48.3	106	51.7	
Treatment status of participants infected with COVID-19					
Without medication	4	21.1	15	78.9	0.061
Outpatient treatment	13	48.1	14	51.9	
Having relatives infected with COVID-19					
Yes	72	41.1	103	58.9	**0.014**
No	44	57.9	32	42.1	
Treatment status of their relatives infected with COVID-19					
Without medication	7	41.2	10	58.8	**0.031**
Outpatient treatment	37	33.3	74	66.7	
Inpatient treatment	12	63.2	7	36.8	
Intensive care treatment	7	70.0	3	30.0	
Death	9	50.0	9	50.0	
Participants' academic years of medical education					
First year	10	21.7	36	78.3	**0.004**
Second year	24	52.2	22	47.8	
Third year	26	45.6	31	54.4	
Fourth year	38	57.6	28	42.4	
Fifth year	18	50.0	18	50.0	
Receiving training on the use of PPE					
Yes	74	43.5	96	56.5	0.216
No	42	51.9	39	48.1	

Table 1. continued

	Participants who have fear of infecting with COVID-19		Participants who have not fear of infecting with COVID-19		p
	N	%	N	%	
Thinking that using PPE is sufficient to protect against COVID-19 Yes No	 62 54	 38.3 60.7	 100 35	 61.7 39.3	**0.001**
Thinking that their institutions will not have problems in the supply of PPE Yes No	 45 71	 36.0 56.3	 80 55	 64.0 43.7	**0.001**
The state of choosing the medical faculty themself Yes No	 103 13	 45.2 56.5	 125 10	 54.8 43.5	0.298
Knowing the risks of the medical profession before the pandemic Yes No	 58 58	 39.7 55.2	 88 47	 60.3 44.8	**0.015**
Thinking that medical education has been disrupted due to the pandemic Yes No	 86 30	 42.8 60.0	 115 20	 57.2 40.0	**0.029**
Increased professional motivation during the pandemic Yes No	 72 44	 45.0 48.4	 88 47	 55.0 51.6	0.609
Changing specialization preference due to pandemic Yes No	 25 91	 69,4 42.3	 11 124	 30.6 57.7	**0.003**
Specializations preferred by participants whose specialization preferences have changed due to the pandemic Specialties with few or no shifts Specialties not in contact with the patient Specialties dealing with COVID-19 infection in the frontlines	 15 5 5	 65.2 71.4 83.3	 8 2 1	 34.8 28.6 16.7	0.856
Approving the resignation or retirement of physicians during the pandemic Yes No	 100 16	 472 41.0	 112 23	 52.8 59.0	0.479
Considering interruption or dropping out medical education due to the pandemic Yes No	 20 96	 76.9 42.7	 6 129	 23.1 57.3	**0.001**

COVID-19: Coronavirus disease-2019

In the study of Nguyen et al. (14) about the fear of COVID-19 in MFS, the COVID-19 fear scores of the 19-22 age group were found to be significantly higher than the 23-26 age group. In another study conducted with nursing students, the participants were separated as under 25 years old and over and no significant relationship was found between age and COVID-19 fear scores (15). Similarly, in this study, in the age group of 23 years and older, fear of COVID-19 was more common and the means of CAS scores was higher. In our opinion, this may be due to the increase in the level of knowledge about diseases as the academic year of medical faculty increases, as well as the fact that the

Table 2. Relation of the CAS scores with the study data of participants

	CAS score		p
	Mean	SD	
Age			
18-22	0.87	1.925	**0.002**
⩾23	2.08	3.323	
Gender			
Male	0.62	1.625	**<0.001**
Female	1.53	2.687	
Having a chronic disease			
Yes	1.55	2.283	**0.044**
No	1.01	2.239	
Smoking			
Yes	1.17	2.452	0.549
No	1.03	2.197	
Living ...			
Alone	1.21	1.578	0.473
With friends	1.16	1.500	
With family	0.98	2.135	
In dormitory	1.55	3.713	
Living with a person whom has a chronic disease			
Yes	1.04	2.161	0.771
No	1.07	2.283	
Status of infected with COVID-19			
Yes	1.00	2.160	0.936
No	1.07	2.266	
Treatment status of participants infected with COVID-19			
Without medication	1.53	2.480	**0.033**
Outpatient treatment	0.63	1.864	
Having relatives infected with COVID-19			
Yes	1.07	2.069	0.283
No	1.04	2.615	
Treatment status of their relatives infected with COVID-19			
Without medication	1.12	2.497	0.755
Outpatient treatment	1.05	1.870	
Inpatient treatment	1.16	2.794	
Intensive care treatment	1.20	1.549	
Death	1.00	2.401	
Participants' academic years of medical education			
First year	0.78	1.590	0.508
Second year	1.28	2.146	
Third year	0.98	2.468	
Fourth year	0.95	2.011	
Fifth year	1.44	3.028	
Receiving training on the use of PPE			
Yes	0.91	2.018	0.095
No	1.38	2.639	
Thinking that using PPE is sufficient to protect against COVID-19			
Yes	0.86	2.073	**0.034**
No	1.43	2.495	
Thinking that their institutions will not have problems in the supply of PPE			
Yes	0.80	1.751	0.139
No	1.32	2.625	
The state of choosing the medical faculty themself			
Yes	1.05	2.312	0.104
No	1.13	1.424	
Knowing the risks of the medical profession before the pandemic			
Yes	1.17	2.320	0.296
No	0.90	2.133	
Fear of infecting with COVID-19			
Yes	1.80	2.817	**<0.001**
No	0.42	1.301	
Thinking that medical education has been disrupted due to the pandemic			
Yes	1.07	2.311	0.854
No	1.00	1.969	
Increased professional motivation during the pandemic			
Yes	1.16	2.453	0.808
No	0.89	1.816	
Changing specialization preference due to pandemic			
Yes	2.53	3.768	**<0.001**
No	0.81	1.770	
Specializations preferred by participants whose specialization preferences have changed due to the pandemic			
Specialties with few or no shifts	2.00	3.162	0.134
Specialties not in contact with the patient	5.43	5.740	
Specialties dealing with COVID-19 infection in the frontlines	1.17	0.753	
Approving there signation or retirement of physicians during the pandemic			
Yes	1.06	2.162	0.362
No	1.05	2.675	
Considering interruption or dropping out medical education due to the pandemic			
Yes	1.85	2.257	**0.003**
No	0.97	2.229	

CAS: Coronavirus anxiety scale, SD: Standard deviation, COVID-19: Coronavirus disease-2019

medical students started to work actively in the hospital due to their internships in the following years of medical education. As a matter of fact, the fear of infecting with COVID-19 in our study was at least among first-year MFS.

In a study conducted with the COVID-19 fear scale in the general population of 772 people in Cuba, it was determined that women had higher COVID-19 fear scores than men (16). Similar to the general population, in another study conducted with MFS, the level of fear of COVID-19 was found to be higher in women than in men (17). Similarly, in another study conducted with nurses in China, women were found to have a higher level of fear of COVID-19 than men (18). In this study, in line with the literature, fear of COVID-19 was found more frequently in women than in men. In addition, in our study, CAS scores in women were found to be statistically significantly higher than in men. While no difference was found between genders in anxiety levels in a study conducted by Cao et al. (8) with MFS, in another study conducted with university students using the self-rating anxiety scale in China, higher anxiety levels were found in female students (19). In another study using the state and trait anxiety scale with MFS in Turkey, it was found that women had higher anxiety scores than men (13). Anxiety disorder is higher in women than men, not only during the pandemic period, but this difference is thought to be related to the fact that women have more serotonin receptors than men, but less serotonin-binding protein (20).

In a study conducted by Sakib et al. (21) in Bangladesh, no relationship was found between having a chronic disease and fear of COVID-19 in healthcare workers; COVID-19 fear levels of healthcare workers who stated that they felt insecure themself and their family members due to COVID-19 were found to be statistically significantly higher. In our study, while no relationship was found between having a chronic disease and fear of COVID-19, the coronavirus anxiety form scores were higher in MFS with chronic diseases, in addition there was a relationship between fear of COVID-19 and living with a person whom has a chronic disease. This situation can be considered as an indication that individuals can accept the risk of COVID-19 contamination due to their profession, even if it creates anxiety for them, but they cannot conscientiously accept the risk of infecting their relatives and they are more afraid of. As a matter of fact, we had health workers who did not go to their homes due to the pandemic and stayed in the allocated places and did not meet with their families. In addition, in another study conducted with MFS, similar to our study, a significant relationship was found between fear of COVID-19 and family members having previously had COVID-19 (22).

While no relationship was found between the students' receiving training on the use of PPE and the fear of COVID-19, the rates of fear of COVID-19 were statistically higher in those who thought that the use of PPE was insufficient to protect against COVID-19 and that their institutions might have problems in providing PPE. In a study conducted with nursing students on the fear of COVID-19 and the use of PPE, it was determined that the COVID-19 fear scores of nursing students who were provided with PPE in the workplace were significantly lower than those who experienced lack of PPE (15). In another study conducted with healthcare professionals, the reasons why healthcare professionals think they have a higher risk of infecting with COVID-19 than other people were questioned, and the most common answer was that PPE is not always available (23). In addition, in our study, the coronavirus anxiety form scores were significantly higher in those who thought that PPE would be insufficient to protect against COVID-19. In the literature, it has been determined that MFS who think that they cannot take adequate precautions against COVID-19 have high state and trait anxiety scores (13). It is considered that this is due to the idea that PPE is the only barrier between this infection without effective treatment and healthcare workers, and that they are unprepared for a sudden outbreak.

Although 90.8% of the MFS in our study stated that they chose to study medicine themself, 41.8% (n=105) of them stated that they were not aware of the professional risks of medicine before the COVID-19 pandemic. Fear of COVID-19 was found to be higher in those who stated that they did not know enough about the risks of the medical profession before the pandemic, and this shows that there is a lack of information about the professions before choosing a profession. The training given before the choice of profession can enable the person to choose a suitable profession and be aware of the risks of the chosen profession, and also increase the professional satisfaction of the person (24).

A statistically significant relationship was found between experiencing fear and anxiety due to COVID-19, and changes in specialty preferences, and even considering interruption or dropping out medical education. It can be predicted that the pandemic may have negative effects on the medical profession and preferences for some specializations.

Conclusion

CAS increased with age, female gender, having a chronic disease, fear of infecting with COVID-19 and not thinking that using PPE is sufficient to protect against COVID-19.

Increase of CAS was changed in specialty preferences of MFS and increased interruption or dropping out medical education.

Meetings should be organized for MFSs to reduce anxiety and fear during the pandemic period.

Ethics

Ethics Committee Approval: The protocol of this study was approved by the Ethics Committee of University of Health Sciences Turkey on 04/12/2020 (number: E-46418926-050.01.04).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Y.U., G.B., G.Z.Ö., E.Ç., Design: Y.U., G.B., M.T.E., E.Ç., Data Collection or Processing: Y.U., G.B., G.Z.Ö., M.T.E., E.Ç., Analysis or Interpretation: Y.U., G.Z.Ö., M.T.E., E.Ç., Literature Search: Y.U., G.B., G.Z.Ö., M.T.E., E.Ç., Writing: Y.U., G.B., G.Z.Ö., M.T.E.

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