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From The Editor In Chief

The upcoming education activities of Turkish Geriatrics Society are;

The 4th course on scientific research in the field of geriatrics which will be held on the 21st, Sept, 2019 in Ankara.Trainers who are experienced in research methodology and scientific writing in geriatrics and gerontology will take part during this interactive course, aiming to support the young academicians and to increase the awareness about geriatric research.

The 7th Geriatrics and Gerontology course, organized by Turkish Geriatrics Society and Hacettepe University Research Center of Geriatrics Sciences-GEBAM by the support of International Institute on Ageing-INIA wiil be held in March 2-6, 2019 in Ankara. All the aspects of geriatrics and gerontology will be discussed by the experienced academicians.

The details of these courses are announced on the website of Turkish Geriatrics Society and the board of directors is honored to invite you to these scientific events.

Prof. Yeşim GOKCE KUTSAL, M.D.
Editor in Chief

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REVIEW ARTICLE

DRY EYE SYNDROME: AN INCREASING PROBLEM WITH AGING

Abstract

Dry eye syndrome is a multifactorial and prevalent ocular disease in elderly population that results in decrease quality of life. Dry eye syndrome is defined as a disease of tear film layer due to reduced tear production and/or tear film instability. Age-related alterations including eyelid laxity, meibomian gland disease and orifice metaplasia, decrease in tear volume result in dry eye. All ages may be suffered from Dry eye syndrome can be seen secondary to another eye diseases or systemic disease. This review will summarize the current knowledge about dry eye and therapeutic interventions being used to treat Dry eye syndrome.

Keywords: Dry eye syndrome; Aging; Sjögrens syndrome

DERLEME MAKALE

KURU GÖZ SENDROMU: YAŞLANMA İLE ARTAN BİR PROBLEM

Öz

Kuru göz sendromu yaşlı popülasyonda sık görülen ve yaşam kalitesinde azalma ile sonuçlanan multifaktöryel bir hastalıktır. Kuru göz sendromu azalmış gözyaşı üretimi ve/veya gözyaşı film tabakasının kararsızlığı nedeni ile gelişen gözyaşı film tabakasının bir hastalığıdır. Göz kapaklarında gevşeklik, meibomian bez hastalığı ve bez orifislerinde metaplazi, gözyaşı haciminde azalma gibi yaşa bağlı değişimler kuru göz ile sonuçlanmaktadır. Kuru göz sendromu tüm yaşları etkileyebilmekte ve göz veya sistemik hastalıklara sekonder ortaya çıkabilmektedir. Bu derlemenin amacı Kuru göz sendromu ile ilgili güncel bilginin ve günümüz tedavi yöntemlerinin özetlenmesidir.

Anahtar sözcükler: Kuru göz sendromu; Yaşlanma; Sjögren sendromu

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INTRODUCTION

Dry eye syndrome (DES) is a multifactorial and prevalent ocular disease in elderly population that results in decrease quality of life. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.(1) DES is defined as a disease of tear film layer due to reduced tear production and/or tear film instability. All ages may be suffered from DES can be seen secondary to another eye diseases or systemic disease. Tear production is controlled by the LFU consisting of the ocular surface (conjunctiva, cornea, accessory lacrimal glands, and meibomian glands), the main lacrimal gland and the interconnecting innervation. (2) Any of these structures may be affected in DES.

Epidemiology

The Tear Film and Ocular Surface Society (TFOS) epidemiology subcommittee reviewed the prevalence, incidence, risk factors, natural history, morbidity and questionnaires reported in epidemiological studies of DES.(3) In 2007 Dry Eye Workshop (DEWS) group reported the prevelance of DES ranged from %5-30 in individuals over the age of 50.(4) Race is an important factor in the prevalence estimates of abnormal tear function. DES's prevelance especially meibomian gland disease (MGD) appears to be higher in Asian than in Caucasian populations, increases with age, and women having a higher prevalence of dry eye than me.(5, 6) The Beaver Dam Eye Study established in a Caucasian population aged 48-91 that 13.3% (95% CI 12.0 -14.7%) of individuals developed symptomatic DES over 5 years and 21.6% (95% CI 19.9-23.3%) over 10 years.(7) Incidence was higher in women (25%) than men (17.3%) over the 10-year period after adjusting for age. Age was a risk factor for increased incidence, with an odds ratio of 1.2x (1.1-1.3) for each 10-year increment.(7)

The Singapore Malay Study and the Spanish Salnes Eye Study showed a higher rate of MGD in men.(8, 9) Interestingly DES is the relatively high prevalence rates reported in younger subjects and in school children, which support the potential risk factors such as digital device use. The Women's Health Study, a study in which 25 665 postmenopausal women provided that women who use HRT, especially estrogen alone, are at increased risk of dry eye syndrome.(10)

Pathophysiology

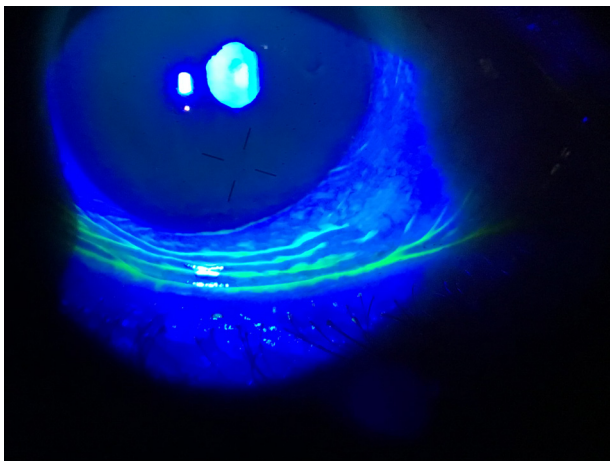
Dysfunction of LFU results in bad quality and poor maintained tear film that causes ocular irritation symptoms and damage to the ocular surface. (11,12) The tear film is highly stabil and the stabil preocular tear film is important for cornea. In response to hyperosmolarity and surface cooling occurring in MGD-related DES, where the lacrimal gland is healthy, DES with a ''wet dry eye". (13) In TFOS-DEWS II report, tear film osmolarity is a central factor in the pathogenesis of aqueous deficiency and evaporative dry eye. (14) The risk factors for DES can be classified as high, moderate and low level of evidence. High level evidence risk factors including; age, female sex, postmenopausal estrogen therapy, antihistamines, collagen vascular disease, corneal refractive surgery, irradiation, hematopoietic stem call transplantation, vitamin A deficiency, hepatitis C and androgen insufficiency, moderate level evidence risk factors including; medications such as tricyclic antidepressants, selective serotonin reuptake inhibitors, diuretics, beta-blockers, diabetes mellitus, HIV/HTLV1 infection, systemic chemotherapy, cataract surgery with a large incision, keratoplasty, isotretinoin, low air humidity, sarcoidosis, ovarian dysfunction and low level evidence risk factors are smoking, hispanic ethnicity, anticholinergic drugs such as anxiolytics, antipsychotics, topical anti-glaucomatous medications, alcohol, menopause, botulinum toxin injection, acne, gout, oral contraceptives, pregnancy. (15-18)

Symptoms of DES

Visual symptoms due to tear film instability and breakup, ocular discomfort, reduced lubrication, and neuropathic pain can be seen with DES. Slit

lamp examination may reveal duct dilatation and gland loss of meibomian glands, punctate epithelial keratopathy, filamentary keratitis, superior limbic keratoconjunctivitis, lid parallel conjunctival folds (LIPCOF) (Figure 1), and the lid margins changes.

Figure 1. The redundant conjunctival folds are located over the free edge of the lower eyelid and stained with fluorescein dye and cobalt light.



Classification of DES

Visual symptoms due to tear film instability and breakup, ocular discomfort, reduced lubrication, and neuropathic pain can be seen with DES. Slit

I. Aqueous-deficient dry eye (ADDE)

ADDE is included Sjögren syndrome dry eye (SSDE) and non-Sjögren syndrome dry eye (NSDE).

1. Sjögren Syndrome and Sjögren Syndrome dry eye

   Sjögren syndrome (SS) is a chronic autoimmune disorder characterized by immune cell infiltration of exocrine glands and systemic complications due to autoantibody production, immune complex deposition and lymphocytic infiltration of many organ. (19, 20)

   Sjögren syndrome occurs predominantly in women, with a female/male ratio of 9:1, and it may lead to a very severe form of DES.(20-23) The lacrimal and salivary ducts are primary targets. Infiltration by T and B lymphocytes, dendritic cells, macrophages and other mononuclear cells, leading to tissue dysfunction or destruction. The loss of aqueous tear flow in Sjögren syndrome is a result of inflammatory cell infiltration of the lacrimal glands which leads to acinar and duct destruction. (19)

2. Non-Sjögren Syndrome dry eye:

   a. Age-related NSDE

   b. Congenital alacrima

   c. Familial dysautonomia

   d. Lacrimal gland infiltration (lymphoma, sarcoidosis, hemochromatosis, and amyloidosis)

   e. Viral infections (retroviruses, Epstein-Barr virus, human T-cell lymphotropic virus type 1, and human immunodeficiency virus (HIV), Hepatitis C virüs (HCV)

   f. Hematopoietic stem cell transplants with or without the development of graft-versus-host disease: infiltration and fibrosis of the lacrimal glands and conjunctiva as a result of T-cell interaction with fibroblasts (20-30).

II. Evaporative dry eye (EDE)

   1. Lid-related evaporative dry eye (intrinsic EDE):

   a. Age-related meibomian gland changes: meibomian gland drop out score is increasing after 40 years of age.

   b. The influence of sex hormones on meibomian gland function: Sjögren syndrome, antiandrogen treatment and complete androgen insensitivity syndrome, is associated with MGD, altered meibum lipid profiles and evidence of decreased tear film stability.

   c. Meibomian gland dysfunction: This is the

most common etiology of EDE. It must be distinguished from other meibomian gland diseases.

i. High meibum delivery state meibomian seborrhea: It is uncommon. This is associated with seborhoeic dermatitis and rosacea. Acne Rosacea is a disease of eye and skin an is usually seen with fairly skinned individuals. Rosacea may be difficult to diagnose and differential diagnosis. Visualize telangiectasia or facial flushing are the skin findings and in eyes chronic recurrent blepharokeratoconjunctivitis, punctate erosions, peripheral keratitis, MGD, or recurrent chalazia are common findings. Children with ocular rosacea often present with corneal involvement and asymmetry of ocular disease, and the potential for sight-threatening visual impairment should be considered.

ii. Low meibum delivery states - obstructive meibomian gland dysfunction: This is obstructive MGD and the most common type. TFOS Workshop on MGD, as follows and further details may be found in that report: "meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/ quantitative changes in the glandular secretion. This may resuls in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease". MGD can be seen primary or secondary also cicatricial or noncictaricial.

2. Disorders of lid aperture, congruity and dynamics

a. Nocturnal lagophthalmos

b. Incomplete lid closure or lid deformity

c. An increase in palpebral fissure width or globe prominence exposes the tear film to greater evaporation

d. Parkinson's disease and in progressive ophthalmoplegia

3. Ocular surface-related evaporative dry eye

a. Allergic eye disease

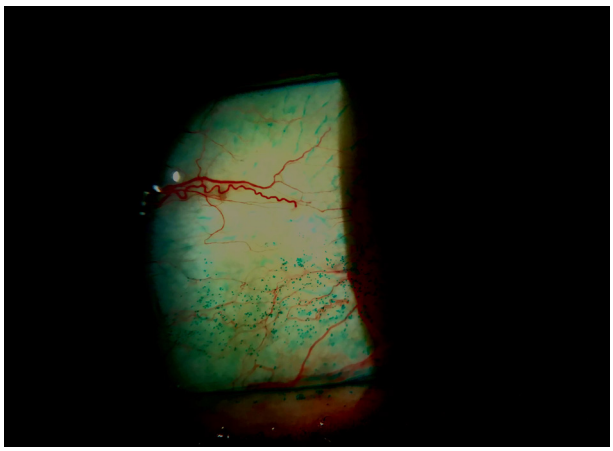
b. Vitamin A deficiency

c. Ocular surface disease due to topical agents (31-40).

Diagnosis of DES

Understanding characteristics of the causative factors, such as environments (air travel, sitting near an air conditioner vent, low humidity), prolonged visual efforts (reading, computer use), or symptomatic treatment with the use of artificial tears is helpful in diagnosing DES. A detailed review system examination must be done for any patient who has significant dry eye. Rheumatological system examination is important. For patients who are suspected of having Sjögrens syndrome, a serological examination (Sjögrens syndrome A antibody (SSA or anti-Ro), anti-Sjögren syndrome B antibody (SSB or anti-La), rheumatoid factor, and antinuclear antibody) should be ordered. Patients who might have thyroid eye disease should be tested for antithyroid peroxidase antibody and antithyroglobulin antibody. For standardization in clinical research, symptoms are typically taken through the use of questionnaire instruments that are most often self-administered by the patient or research subject without input from the clinician or researcher. Tear film breakup time, Schirmer test, ocular surface staining, tear film osmolarity, impression cytology, meibography, and in vivo confocal microscopy are the current diagnostic tests. (Figure 2).

Figure 2. Lissamine green staining of the ocular surface in a patient with dry eye syndrome secondary to Sjogrens Syndrome.



Treatment of DES

Staged Management And Treatment Recommendations For DES

First step of the management include education about the disease, modification of local environmental factors, dietary modifications (including oral essential fatty acid supplementation), identification and potential modification/elimination of offending systemic and topical medications. As treatment, ocular lubricants of various types (if MGD is present, then consider lipid-containing supplements), and lid hygiene and warm compresses comprise the treatment of mild DES. If the above options are inadequate, the second step of the treatment of DES incule non-preserved ocular lubricants to minimize preservative-induced toxicity, tea tree oil treatment for Demodex (if present) and inflammation, punctal occlusion and/or moisture chamber spectacles/goggles to tear conservation, and overnight treatments (such as ointment or moisture chamber devices). For inflammatory DES, such as Sjögrens Syndrome, the gold standart treatment options are anti-inflammatory agents including topical corticosteroid for limited-duration non-glucocorticoid immunomodulatory eye drops (such as cyclosporine and LFA-1 antagonist). For the severe DES, to protect the ocular surface, autologous/allogeneic serum eye drops, therapeutic contact lenses or some surgical procedures (tarsorrhaphy, amniotic membrane grafts) can be considered (41, 42).

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RESEARCH

RELATIONSHIP BETWEEN FIBRINOGEN -TO- ALBUMIN RATIO AND ANGIOGRAPHIC NO-REFLOW IN ELDERLY PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION TREATED WITH PRIMARY PERCUTANEOUS CORONARY İNTERVENTION

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Abstract

Introduction: Primary percutaneous coronary intervention carries a low success rate and high procedural risk in elderly patients. No-reflow is a serious complication of primary percutaneous coronary intervention in the treatment of acute ST- elevation myocardial infarction. We evaluated whether admission fibrinogen-to-albumin ratio, which has emerged as an inflammatory and haemorheological marker for predicting adverse outcomes in some cardiovascular diseases, predicts angiographic no-reflow in elderly patients with ST-elevation myocardial infarction.

Materials and Method: In total, 617 patients (78.1% men; median age, 75 (68-80years) who underwent primary percutaneous coronary intervention and were admitted within 12 hours from the onset of symptoms were classified into two groups based on the final thrombolysis in myocardial infarction flow grading. No-reflow was defined as post-percutaneous coronary intervention thrombolysis in myocardial infarction grade 0, 1 and 2, and angiographic success (normal reflow) was defined as thrombolysis in myocardial infarction grade 3.

Results: Of the total, 29 (51.8%) patients were found to be frail, 22 (39.3%) were found to be prefrail, and 5 (8.9%) were found be nonfrail. Further, 34 (60.8%) patients were at the risk of malnutrition. Additionally, 38 (67.8%) patients had delirium and 8 (14%) patients died during the postoperative month 1. Although Nutritional Risk Screening 2002 scores positively correlated with first-month mortality, no correlation was found between malnutrition and delirium status. A positive correlation was found between clinical frailty scale score and delirium; however, there was no correlation between clinical frailty scale score and first-month mortality. Positive predictive values of malnutrition and frailty together for first-month mortality increased up to 54.5% from 17.6% and 13.6 and that of delirium increased to 80.2% from 54.5% and 72.4%, respectively.

Conclusion: The incidence of angiographic no-reflow was 19.9% (n = 123). Patients with no-reflow had higher rates of diabetes and smoking, higher thrombus burden and Killip class≥2 on admission and lower baseline left ventricular ejection fraction; they also had increased white blood cell counts, C-reactive protein and fibrinogen-to-albumin ratio levels at admission than the normal flow group. In multivariate analysis, white blood cell count, smoking and fibrinogen-to-albumin ratio were independent predictors of angiographic no-reflow.

Keywords: Aged; Fibrinogen; No-reflow phenomenon; Percutaneous coronary intervention; Serum albumin; St elevation myocardial infarction

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İLERİ YAŞTA ST YÜKSELMELİ MİYOKARD ENFARKTÜSÜ İLE BAŞVURAN VE PRİMER PERKÜTAN KORONER GİRİŞİM YAPILAN HASTALARDA ANJİYOGRAFİK NO-REFLOW İLE FİBRİNOJEN / ALBÜMİN ORANI ARASINDAKİ İLİŞKİ

Öz

Giriş: Genç hastalarla karşılaştırıldığında, ileri yaş hastalarda primer perkütan koroner girişim, daha düşük başarı ve artmış prosedürel komplikasyonlarla ilişkilidir. No-reflow fenomeni, ST- yükselmeli miyokard enfarktüsü ile primer perkütan koroner girişim yapılan hastalarda karşılaşılabilecek en ciddi komplikasyonlardan biridir. Fibrinojen / albümin oranı; bazı kardiyovasküler hastalıklarda istenmeyen sonlanımları öngördüren, inflamasyon ve hemoreolojiyi yansıtan bir parametre olarak ortaya çıkmıştır. Biz bu çalışmada ST-yükselmeli miyokard enfarktüsü ile başvuran yaşlı hastalarda, başvuru sırasındaki fibrinojen / albümin oranının anjiyografik no-reflow üzerindeki öngördürücülüğünü değerlendirmeyi amaçladık.

Gereç ve Yöntem: Semptom başlangıcından sonra 12 saat içerisinde başvurup primer perkütan koroner girişim yapılan toplam 617 hasta (%78.1 erkek, ortanca yaş: 75 (68-80) yıl) çalışmaya dahil edildi. Hastalar nihai Miyokard Enfarktüsünde Tromboliz akımlarına göre iki gruba ayrıldı. No-reflow işlem sonrası Miyokard Enfarktüsünde Tromboliz 0, 1 ve 2 akım saptanması, anjiyografik başarı ise Miyokard Enfarktüsünde Tromboliz 3 akım saptanması olarak belirlendi.

Bulgular: Anjiyografik no-reflow'un insidansı %19.9 (n =123) olarak saptandı. No-reflow gelişen hastalarda, normal akım grubuna kıyasla hipertansiyon, sigara içiciliği daha sık, trombüs yükü daha fazla ve başvuruda Killip sınıflaması ≥ 2 olma oranı daha yüksek, bazal ejeksiyon fraksiyonu daha düşük, beyaz kan hücre sayısı, yüksek duyarlıklı C-reaktif protein ve fibrinojen/albümin oranı daha yüksek saptandı. Çok değişkenli analizde; beyaz kan hücre sayısı, sigara ve fibrinojen/albümin oranı no-reflow'un bağımsız belirteçleri olarak bulundu.

Sonuç: Sonuç olarak, ST - yükselmeli miyokard enfarktüsü ile başvuran ve perkütan koroner girişim yapılan ileri yaş hastalarda, başvurudaki fibrinojen/albümin oranı anjiyografik no-reflow'un güçlü ve bağımsız bir belirtecidir.

Anahtar sözcükler: Fibrinojen, No-reflow fenomeni; Perkütan koroner girişim; Serum albümini; St yükselmeli miyokard enfarktüsü; Yaşlı

INTRODUCTION

Cardiovascular disorders are the leading cause of morbidity and mortality in persons aged ≥ 65 years; the incidence of these diseases increases with age (1). The elderly population constitutes a growing proportion of patients with acute coronary syndrome (ACS), which includes ST-elevation myocardial infarction (STEMI) (2). Currently, primary percutaneous coronary intervention (PCI) is the preferred way of reperfusion for STEMI, also in elderly patients (3). However, primary PCI carries a low success rate and high procedural risk in older patients than in younger ones. Elderly patients not only possess baseline high-risk features for adverse cardiac events but also have poor procedural characteristics, including poor interventional success and decreased myocardial blush grade, ST-segment resolution and low post-PCI thrombolysis in myocardial infarction (TIMI) grade 3 blood flow (flow grades based on results of the TIMI trial), also called the no-reflow phenomenon (4).

No-reflow is a serious complication of acute STEMI undergoing PCI and is related to larger infarct size and short- and long-term morbidity and mortality (5). The no-reflow phenomenon represents an acute diminution in coronary blood flow despite the presence of normal epicardial coronary artery patency (6). The specific pathophysiological mechanism for its occurrence is still not clearly elucidated, and it is believed that platelet activation and inflammation play a major role in evolving no-reflow (7). Recently, fibrinogen-to-albumin ratio (FAR) has emerged as a feasible and valuable serological marker that may reflect haemorheological and inflammatory status. Elevated FAR concentration has been demonstrated in some cardiovascular diseases and is significantly associated with the severity of coronary stenosis in patients with STEMI (8). To the best of our knowledge, only a limited number of investigations have evaluated the relationship between inflammatory and haemorheological markers such as the CRP, albümin, fibrinogen, FAR and angiographic no-reflow. Moreover, most studies looking at the role of inflammation in no-reflow have been carried out in all-age groups (9, 10), and elderly patients were under-represented in these studies. Therefore this study aimed to investigate the association of inflammatory and hemorheological markers such as fibrinogen, albumin, CRP, FAR with angiographic no-reflow in elderly patients with STEMI in an attempt to explore the predictive value of these indices especially FAR as a novel predictor for elderly AMI patients.

MATERIALS AND METHOD

Study population

The present investigation was a single-center, observational, retrospective cohort study among consecutive elderly patients who were admitted to our tertiary centre with acute STEMI within 12 h of symptom onset and underwent primary PCI between January 2015 and March 2017. All patients were at least 65 years of age. STEMI was defined based on the criteria determined by the European Society of Cardiology and the American College of Cardiology guidelines and was described as classic symptoms of coronary ischaemia for more than 30 min and detection of ST-segment elevation of ≥2.0 mm in men and ≥1.5 mm in women in leads V2–V3 and/or ≥1.0 mm ST-segment elevation in other two contiguous electrocardiography leads or on the presence of a new (or possibly new) left bundle branch block. Patients fulfilling the following criteria were excluded from the study: severe valvular disease, previous history of coronary artery bypass graft, treatment with fibrinolytic agents, cardiogenic shock, renal or hepatic insufficiency, active infection, haematological proliferative diseases, oncological or inflammatory disorders and having no recorded measurement of admission laboratory parameters. The study complied with the principles outlined in the Declaration of Helsinki and was approved by the local ethics committee of our hospital.

Definitions and study endpoints

Hypertension was defined as systolic blood

pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or use of antihypertensive medications. Diabetes was defined as overnight fasting blood glucose ≥126 mg/dL or use of insulin or oral hypoglycaemic agents. Dyslipidaemia was defined as total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >130 mg/dL, Triglycerides >150 mg/dl or use of lipid-lowering drugs. Family history of coronary artery disease (CAD) was defined as having a first-degree male relative who developed CAD before the age of 55 or a first-degree female relative who developed CAD before the age of 65. Patients were classified as smokers if they were actively smoking or had quit smoking within the previous year. The primary endpoint was accepted as the occurrence of no-reflow. Accordingly, the study population were subdivided into normal flow group and no-reflow group.

Laboratory parameters

Peripheral venous blood samples from all patients at the emergency department were collected in tubes with EDTA for haematological tests and dry tubes for biochemical tests and were analysed on priority. Complete blood count measurements were determined using an automated hematology analyzer XE-1200 (Sysmex, Kobe, Japan). Biochemical measurements were performed using a molecular analyzer (Roche Diagnostics, Manheim, Germany). Plasma fibrinogen concentrations were measured using an automatic coagulation analyzer (STA Compact Max, Stago, France). Baseline FAR was calculated using the statistical program (SPSS) by dividing the fibrinogen value with the albumin value.

Echocardiography

Baseline two-dimensional and Doppler echocardiographic examination was performed by experienced echocardiographers for all patients in the intensive coronary care unit to evaluate left ventricular ejection fraction (LVEF) within the first 24–48 h using the same commercially available ultrasound equipment.

Coronary angiography and primary PCI procedure

All primary PCI procedures were performed in our high-volume tertiary cardiology centre with 24 h/7 days PCI facility by expert operators according to the current practice guidelines. Unfractionated heparin 100 U/kg and aspirin 300 mg plus clopidogrel (loading dose 600 mg) were administered to all patients once diagnosed with STEMI in the emergency department. Average door-to-balloon duration was <30 min. Procedural decisions such as stent type, size and length selection and use of adjunctive pharmacotherapy (including glycoprotein IIb/IIIa receptor antagonists) were made by the procedure operators. After stenting, all patients received dual antiplatelet treatment with acetylsalicylic acid (100 mg daily) and clopidogrel (75 mg daily) and were advised to continue these medications for at least 12 months. The TIMI flow grades were evaluated by two interventional cardiologists blinded to the clinical data. The angiographic no-reflow phenomenon was accepted in patients with anterograde TIMI flow grade ≤2 once the recanalisation of the vessel was performed in the absence of dissection, thrombus, spasm or distal embolisation in the final angiogram. Although there is no standard therapy for no-reflow, patients who had no-reflow were treated according to general practice. Intracoronary vasodilatators, glicoprotein IIb/IIIa inhibitor and aspiration thrombectomy were administered at the discretion of the operator.

Multivessel disease was described as presence of ≥1 lesion with >50% stenosis in ≥1 major epicardial coronary artery or its major branches distant from the infarct related artery. To assess thrombus burden we used the TIMI thrombus scale (11). TIMI thrombus grade 0, no angiographic characteristics of thrombus are present; TIMI thrombus grade 1, possible thrombus with angiographic characteristics include declined contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus; TIMI thrombus grade 2, definite

thrombus is present in multiple angiographic views, with the largest dimensions ≤1/2 the vessel diameter; in TIMI thrombus grade 3, definite thrombus in multiple views but with the greatest linear dimension>1/2 but <2 vessel diameters; TIMI thrombus grade 4, definite large thrombus, with the greatest dimension ≥2 vessel diameters; TIMI thrombus grade 5, there is complete thrombotic occlusion of the vessel. TIMI thrombus grade ≥4 was accepted as high grade angiographic thrombus burden (12). Pre-procedural collateral flow was determined according to Rentrop classification: any visible filling of collaterals was considered grade 0, filling of side branches without epicardial segments was classified as grade 1, partial filling of epicardial segments was classified as grade 2, and complete filling of epicardial segments was considered grade 3(9). Rentrop grade 0 and 1was accepted as poor collateral flow (13).

Statistical analysis

Statistical analysis was performed using SPSS 22.0 Statistical Package Program for Windows (SPSS, Inc., IL, USA). Continuous variables were presented as mean ± SD and median with interquartile ranges as appropriate and categorical variables as frequency and percentage. To test normality of distribution, the Kolmogorov–Smirnov test was used. Differences between groups were evaluated using Student's t-test for normally distributed variables and Mann-Whitney U test test for variables without normal distribution. The Chi square or Fisher's exact test was used to compare categorical variables. We first used univariate analysis to examine the association of each variable with angiographic no-reflow. To assess the effects of parameters that were significant in univariate analysis ($p < 0.05$), we used multivariate logistic regression. The receiver operating characteristic (ROC) curve was used to determine an optimal cut-off value for FAR according to the Youden's index. The correlation between FAR and hsCRP was assessed using Spearman's correlation test. A p value of <0.05 (using a two-sided test) was considered significant.

RESULTS

The baseline clinical, laboratory and angiographic characteristics of patients with and without no-reflow are summarised in Table 1. Of 617 patients, 78.1% were male and the median (interquartile range) age was 75 (68–80) years. Angiographic no-reflow was developed in 123 (19.9%) patients. Study patients were divided into two groups based on their TIMI flow grades after primary PCI. Patients with no-reflow exhibited a higher rate of diabetes mellitus, smoking and lower LVEF compared with those without no-reflow. Also no-reflow group had higher thrombus burden and high rates of Killip class ≥2 on admission when compared to that of reflow group. The no-reflow group had significantly higher white blood cell (WBC) counts and fibrinogen and hsCRP levels and lower albumin levels than those in the reflow group.

Patient FAR values were significantly higher in the no-reflow group than in the normal flow group ($p < .001$; Figure 1). There was no statistically significant difference in angiographic characteristics between the two groups.

The ROC curve analysis explored the discriminatory capability of admission FAR for no-reflow. The area under the curve was 0.810 (95% CI, 0.765–0.856; $p < 0.001$). Using a cut-off level of 75.0, FAR predicted angiographic no-reflow with a sensitivity of 76% and specificity of 76% (Figure 2).

Univariate and multivariate logistic regression analyses of the relationship between the no-reflow phenomenon and multiple parameters are listed in Table 2. On univariate logistic regression analysis, the FAR values demonstrated a strong relation with the no-reflow phenomenon ($p < .001$). The other univariate predictors of no-reflow were smoking, diabetes mellitus, LVEF, high TIMI thrombus grade, high Killip class on admission, WBC, hsCRP, fibrinogen and albumin levels. When constructed, a multivariate logistic regression including all the following significant univariate predictors: WBC (odds ratio [OR], 1.679; 95% confidence interval [CI],

1.446–1.949; p <.001); smoking (OR, 1.918; 95% CI, 1.165–3.159; p =.010) and FAR levels >75.0 (OR, 6.968; 95% CI, 4.091–11.869; p <.001) were identified as independent predictors of angiographic no-reflow.

In the correlation analysis, FAR values had a significantly positive correlation with the hsCRP level (r = 0.385, p < 0.001) (Figure 3).

DISCUSSION

This study demonstrated that FAR was independently associated with angiographic no-reflow phenomenon in elderly patients with STEMI. Patients with elevated FAR levels had higher risks for this complication. FAR was also positively correlated with serum hsCRP levels, demonstrating its strong relationship with systemic inflammation.

Elderly patients are at higher risks than younger patients if they present with STEMI. Elderly patients are often frail and have extensive CAD, which elevates the risk of morbidity and mortality. Other reasons for higher risk include atypical presentation and delays in seeking medical care (2). Trials regarding ACS and revascularisation have selectively excluded elderly patients because of potentially high mortality rates. Thus, most of the evidence has been extrapolated from the studies consisting of younger patients, which impedes extending the findings of these studies to the elderly population that experiences the worst cardiac outcomes (14).

It is well known that in elderly patients, the primary PCI success rate is lower than in younger patients; outcomes after the procedure are worse, with higher risks of PCI complications. Despite similar frequencies of TIMI flow before PCI, older patients are less likely to achieve optimal epicardial flow (TIMI grade 3 flow) and ST-segment resolution after PCI (15). The presence of complex coronary anatomy frequently observed in older patients may be associated with a higher rate of distal embolisation, which is a significant determinant of myocardial perfusion and long-term clinical outcome after primary PCI(16). In addition, several studies have underlined that older patients are more likely to have no reflow phenomenon, probably linked to co-morbidities and more severe coronary artery disease (17, 18). De Luca et al demonstrated a relationship between older age and impaired myocardial perfusion evaluated by myocardial blush grade as well as ST-segment resolution. Furthermore, age and poor myocardial flow- perfusion were shown to be independently related with 1-year mortality (19). Therefore, early identification of elderly patients with high risks of impaired myocardial perfusion and coronary angiographic no-reflow is essential.

The pathophysiological mechanisms of coronary no-reflow are presently not exactly understood. Previous studies demonstrated that no-reflow is related to a diverse set of pathological factors, such as coagulation cascade via endothelial dysfunction, microvascular obstruction caused by distal embolisation, action of reactive oxygen species, ischaemia–reperfusion injury, platelet aggregation, haemorheological alterations and complicated interaction between leukocytes and platelets activated by the inflammatory process (20).

Fibrinogen and albumin are widely utilised and are significant factors in responses to systemic inflammatory and haemorheological changes. Fibrinogen is known to be a precursor of fibrin and stimulates platelet aggregation. Fibrinogen is also an acute phase protein with positive pro-inflammatory effects. Fibrinogen was shown to upregulate the synthesis of pro-inflammatory cytokines, including interleukin-1 and tumour necrosis factor alpha. These cytokines inhibit the arrangement of stable fibrous caps and mediate increased adhesion molecule expression; they also culminate in endothelial dysfunction and thrombus formation (21). Therefore, these alterations could further generate the activation and rupture of atherosclerotic plaque and the resulting thrombosis. Additionally, elevated fibrinogen levels are related with increased plasma viscosity, which further causes diminished blood flow velocity and finally increases

the risk of thrombosis (22). Increased concentration of fibrinogen has been shown to increase the risk of thrombosis and is an independent predictor of coronary heart disease and myocardial infarction (MI) according to the findings of previous studies (23).

Serum albumin is the major protein in human serum, which is the main component that maintains plasma oncotic pressure; it participates in acute and chronic inflammatory reactions (24). Albumin is one of the main factors affecting plasma viscosity, which plays an important role in inhibiting platelet activation and aggregation and might negatively correlate with erythrocyte aggregation (25). Previous studies demonstrated that serum albumin levels are closely associated with the occurrence, development and severity of coronary heart disease (26). Recent studies also reported that decreased concentration of albumin is a risk factor for incident acute MI in patients with CAD and is related to elevated cardiovascular morbidity and long-term outcomes (27). Furthermore, hypoalbuminemia can predict the occurrence of the no-flow phenomenon in patients with STEMI after PCI (28).

Based on the previous study results, both elevated fibrinogen levels and lower serum albumin levels were demonstrated to be associated with adverse cardiac outcomes in STEMI. FAR, which comprises these two predictors, is an important serological marker that may provide information on both haemorheology and inflammation in patients with STEMI. It has been shown that there is a positive correlation between FAR and SYNTAX score in patients with STEMI, and FAR can be utilised as an independent marker of elevated SYNTAX score and the severity of coronary stenosis in STEMI [8]. Xiao et al. (29) found that preoperative FAR was an independent prognostic factor in STEMI patients undergoing primary PCI and might improve risk stratification in patients with STEMI. Recently, Zhao et al. (9) reported that admission FAR levels were associated significantly and independently with angiographic no-reflow and short-term mortality in 510 patients with STEMI undergoing pPCI. In addition, fibrinogen and hs-CRP were significantly higher among patients with no-reflow in all-age groups. According to their results, the mean age of the study population was 61.14 ± 11.15 and compared to normal-reflow group, patients in the no-reflow group were significantly older (64.09 ± 11.53 vs.60.44 ± 10.96 years). In another recent study, Del Turco et al. (30) evaluated 625 patients with STEMI and demonstrated that elderly patients had significantly higher values of BNP, leukocytes, CRP-to-albumin ratio (CAR), fibrinogen and lower serum albumin levels compared with young patients. In elderly patients, higher levels of CAR, fibrinogen and leukocytes were significantly associated with no-reflow similar to our study results. Conversely, in young patients, BNP level on admission was the only laboratory parameter associated with no-reflow. Thus their findings showed a differential inflammatory pattern between young and elderly STEMI patients at the hospital admission that confirms the presence of a higher acute proinflammatory systemic response and chronic low-grade inflammatory status typical of aging in elderly patients. In the light of these findings, one may conclude that benefits of FAR, as a combination of fibrinogen and albumin might be more impressive in the aging patients. Therefore, this retrospective study was undertaken to evaluate whether clinical benefits of FAR as predictor of no-reflow in the aged could be validated in the setting of STEMI. As expected, FAR level on admission was found as a strong predictor of no-reflow in elderly patients with STEMI in our study.

Several reports have shown that multivessel disease is frequently associated with no-reflow phenomenon (31). In the current study, there were no differences with respect to the ratio of multivessel disease between no-reflow and reflow groups. It is known that older patients have a higher number of affected vessels compared to younger patients (32). In our study, an age-dependent high frequency of multivessel disease in both groups may be the underlying mechanism of the non-significant effect

of multivessel disease on the presence of no-reflow against the results of previous several studies evaluating all-age groups.

In agreement with the literature, our results suggest that inflammation and haemorheological alterations play an important role in no-reflow pathophysiology and parameters that can directly or indirectly reflect inflammation and that blood viscosity can play a substantial role in the success rate of primary PCI in elderly patients with STEMI. Our results demonstrated that admission FAR levels were significantly higher in the no-reflow group compared with the normal flow group. FAR values predicted the no-reflow phenomenon with good sensitivity and specificity. Clinically, as a new marker of inflammation and haemorheology, FAR may be used to identify patients at a high risk for evolution of no-reflow phenomenon. At present, there is no consensus on how to best manage no-reflow. As no-reflow is related with adverse cardiovascular events, accurate prediction of no-reflow could ameliorate the outcomes of patients by close monitoring. Accurate risk stratification for the occurrence of no-reflow might help deciding on the most effective measures aimed at preventing this entity and using certain techniques that may ameliorate the degree of noreflow in the setting of acute MI. Such prevention strategies include a shortened door-to-balloon time, more effective antiplatelet drug therapies (prasugrel or tikagrelor), primary stenting, avoidance of high pressure stent deployment, and aspiration thrombectomy before the stent implantation in this high-risk population with STEMI (33).

Limitations

This study has some limitations. First, this was a retrospective single-centre study with cross-sectional design. Although a relatively large series of elderly patients with STEMI were examined, the study population was limited in size. This factor may limit the power of statistical analyses. In addition, we did not evaluate several risk factors for the no-reflow phenomenon, and it might have influenced the multivariate test results. We evaluated FAR values only once during admission; potential temporal changes were not examined in this study. Absence of other inflammatory markers, except for hsCRP, was another limitation of this study. We only showed a relationship between FAR and angiographic no-reflow rather than a causal association. Although the purpose of our study was not to investigate the association between FAR and in-hospital mortality, it would be better if we had followed the patients and investigate the relationship between short term mortality and FAR in these patients. Prospectively designed studies on larger elderly cohorts are required to validate our findings, reveal the underlying mechanism and elucidate the utility of FAR in elderly AMI patients.

CONCLUSIONS

This study is the first to focus on the relationship of admission FAR values with angiographic no-reflow among elderly patients with STEMI. Our findings revealed that higher FAR levels were significantly and independently associated with the no-reflow phenomenon.

Furthermore, preprocedural FAR values may be useful in reflecting the inflammatory status and haemorheological alterations in elderly patients. As a low-cost, simple, reproducible parameter, FAR can be used in routine clinical practise in predicting no-reflow. Nevertheless, our findings should be confirmed by prospective and large-scale studies, including other inflammatory biomarkers, to determine the precise role of FAR in elderly patients with STEMI.

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CONFLICTS OF INTEREST

The authors of this article state that they have no conflict of interest.

Table 1. Baseline clinical, laboratory and angographic characteristics of the study population according to the presence of angiographic no-reflow.

Variable	Total n = 617	No-reflow (+) n = 123	No-reflow (–) n = 494	p value
Age	75 (68-80)	76 (68-81)	75 (68-80)	.167
Gender, Male n (%)	482 (78.1 %)	90 (73.2 %)	392 (79.4 %)	.138
Hypertension, n (%)	342 (55.4 %)	62 (50.4 %)	280 (56.7 %)	.210
Diabetes, n (%)	232 (37.6 %)	56 (45.5 %)	176 (35.6 %)	.043
Smoking, n (%)	235 (38.1 %)	59 (48.0 %)	176 (35.6 %)	.012
Hyperlipidemia, n (%)	367 (59.5 %)	82 (66.7%)	285 (57.7 %)	.070
Family History of CAD, n (%)	120 (19.4 %)	24 (19.5 %)	96 (19.4 %)	.984
Body-mass index (kg/m^2)	23.3 ± 2.7	22.9 ± 2.6	23.4 ± 2.7	.093
LVEF (%)	45 (42-50)	43(42-48)	43(40-48)	.027
Heart rate (bpm)	79.9 ± 11.6	81.5 ±10.8	79.5 ± 11.8	.091
Killip class ≥2	162 (26.3 %)	42 (34.1 %)	120 (24.3 %)	.026
Medical therapy				
Aspirin, n (%)	278 (45.1%)	60 (48.8%)	218 (44.1 %)	.354
ß blocker, n (%)	462 (74.9 %)	88 (71.5 %)	374 (75.7%)	.341
Statin, n (%)	299 (48.5 %)	54 (43.9 %)	245 (49.6 %)	.258
ACE inh/ARB n (%)	384 (62.4 %)	72 (59.5%)	312 (63.2%)	.457
Diuretic, n (%)	97 (15.7 %)	23 (18.7 %)	74 (15.0 %)	.311
Angiographic characteristics	2.9 ± 0.3	2.9 ± 0.4	2.9 ± 0.3	.396
Stent length (mm)	20 (18-23)	20 (17-25)	20 (19-23)	.780
Total number of stents	1.8 ± 0.5	1.8 ± 0.5	1.8 ± 0.5	.281
High-grade thrombus burden, n (%)	440 (71.3 %)	99 (80.5 %)	341 (69 %)	.012
Collateral flow ≤1, n (%)	133 (21.6 %)	33 (26.8 %)	100 (20.2 %)	.112
Use of GpIIb/IIIa inhibitor, n (%)	31 (5.0 %)	10 (8.1%)	21 (4.3 %)	.078
Pain to balloon time (min)	301±128	320 ± 133)	296 ± 126	.065

Variable	Total n = 617	No-reflow (+) n = 123	No-reflow (–) n = 494	p value
DES, n (%)	138 (22.4 %)	24 (19.5 %)	114 (23.1%)	.396
Number of affected vessels	1.8 ± 0.5	1.8 ± 0.5	1.9 ± 0.5	.054
Multivessel disease, n (%)	464 (75.2 %)	98 (79.7 %)	366 (74.1 %)	.199
Laboratory parameters				
Hemoglobin (g/dl)	13.9 (12.5-14.9)	14.5 (13.0-15.6)	14.4 (13.0-15.3)	.561
WBC (×103 µL)	8.0 ±1.8	9.3 ±1.5	7.7 ±1.8	<.001
Platelet (×103 µL)	254 ± 69	262 ± 61	253 ± 71	.188
Glucose, mg/dL	101 (91-130)	102 (90-131)	101 (92-130)	.732
Creatinine (mg/dl)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	.072
Urea (mg/dl)	35 (28-43)	33 (28-42)	36 (28-44)	.195
Total cholesterol (mg/dL)	175 ± 41	174 ± 41	175 ± 42	.806
Triglycerides (mg/dL)	141 (100-190)	150 (112-194)	138 (100-186)	.098
LDL cholesterol (mg/dL)	105 (82-130)	101 (80-132)	105 (82-127)	.819
HDL-C (mg/dl)	40 (33-47)	39 (33-45)	40 (33-48)	.444
Albumin (g/dl)	3.9 ± 0.5	3.8 ± 0.7	4.0 ± 0.4	.005
hsCRP (mg/dl)	2.5 (1.2-5.0)	5.0 (2.0-7.0)	2.4 (1.1-4.8)	<.001
Fibrinogen	305 ± 62	318 ± 78	302 ± 56	.011
Fibrinogen to albumin ratio	71 ± 13	83 ± 10	68 ± 11	<.001

Data are presented mean ± SD or n (%).

ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; CAD: coronary artery disease; DES: Drug-eluting stent; HDL-C: high-density lipoprotein cholesterol; FAR: fibrinogen to albümin ratio; HDL-C: high-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; WBC: white blood cell;

Table 2. Univariate and multivariate logistic regression analysis for prediction of angiographic no-reflow.

Variable	OR	Univariate analysis 95 % CI	P Value	OR	Univariate analysis 95 % CI	P Value
Age	1.027	0.997-1.058	0.076			
Gender, male	0.710	0.450-1.118	0.139			
Hypertension	0.777	0.523-1.154	0.211			
Diabetes	1.510	1.013-2.252	0.043	1.333	0.820-2.165	0.246
Smoking	1.666	1.118-2.482	0.012	1.918	1.165-3.159	0.010
Hyperlipidemia	1.467	0.968-2.222	0.071			
Family history of CAD	1.005	0.610-1.655	0.984			
Body-mass index	0.940	0.874-1.010	0.093			
LVEF (%)	0.957	0.921-0.994	0.024	0.979	0.935-1.024	0.348
Heart rate	1.015	0.998-1.032	0.091			
Killip class ≥2	1.798	1.181-2.738	0.006	1.261	0.738-2.156	0.396
Aspirin	1.206	0.812-1.791	0.354			
β-blocker	0.807	0.518-1.256	0.341			
Statin	0.795	0.535-1.183	0.259			
ACE inh /ARB	0.857	0.571-1.287	0.457			
Diuretic	1.305	0.779-2.187	0.312			
Stent diameter	0.788	0.455-1.365	0.396			
Stent lenght	0.993	0.949-1.039	0.757			
Total number of stents	0.814	0.560-1.183	0.280			
Use of Gp2b/3a inhibitor	1.993	0.913-4.350	0.083			
Pain to balloon time	1.001	1.000-1.003	0.066			
DES	0.808	0.494-1.322	0.397			
High-grade thrombus burden	2.179	1.313-3.618	0.003	1.049	0.539-2.042	0.888
Collateral flow ≤1	1.445	0.916-2.278	0.113			
Multivessel disease	1.371	0.846-2.222	0.201			
Number of affected vessels	0.696	0.481-1.007	0.055			

Variable	OR	Univariate analysis 95 % CI	P Value	OR	Univariate analysis 95 % CI	P Value
Hemoglobin (g/dl)	1.071	0.982-1.167	0.122			
Platelet (×103 µL)	1.002	0.999-1.005	0.188			
WBC (×103 µL)	1.756	1.534-2.011	<.001	1.679	1.446-1.949	<.001
Glucose (mg/dl)	0.996	0.995-1.004	0.325			
Creatinine (mg/dl)	1.670	0.798-3.495	0.174			
Urea (mg(dl)	0.999	0.986-1.013	0.937			
Total cholesterol (mg/dl)	0.999	0.995-1.004	0.806			
Triglycerides (mg/dl)	1.002	0.999-1.004	0.147			
LDL cholesterol (mg/dL)	0.999	0.994-1.005	0.838			
HDL-C (mg/dl)	0.996	0.978-1.014	0.644			
Albumin (g/dl)	0.499	0.344-0.725	<.001			
hsCRP (mg/dl)	1.150	1.079-1.226	0.001	0.952-1.134	0.197	
Fibrinogen	1.004	1.001-1.007	0.012			
Fibrinogen to albumin ratio	1.117	1.093-1.142	<.001			
FAR >75.0	10.328	6.489-16.441	<.001	4.091-11.869	<.001	

ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; CAD: coronary artery disease; DES: Drug-eluting stent; HDL-C: high-density lipoprotein cholesterol; FAR: fibrinogen to albümin ratio; HDL-C: high-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; WBC: white blood cell;

Figure 1. Box plot presentation comparison of fibrinogen to albumin ratio.

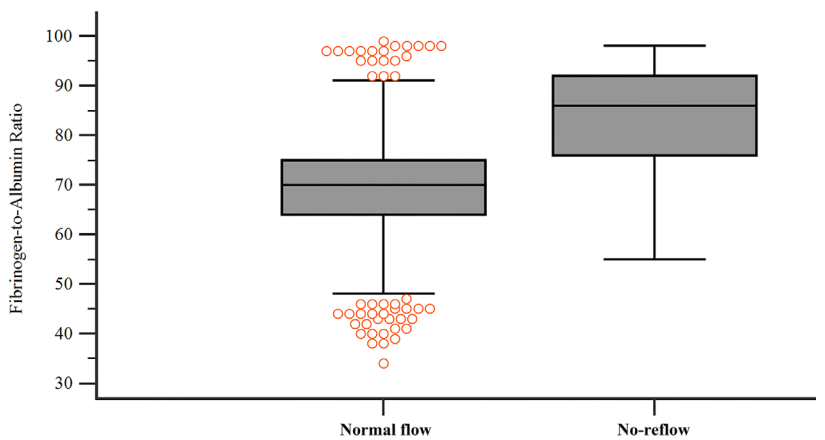


Figure 2. ROC curve analysis of fibrinogen to albumin ratio to predict no-reflow

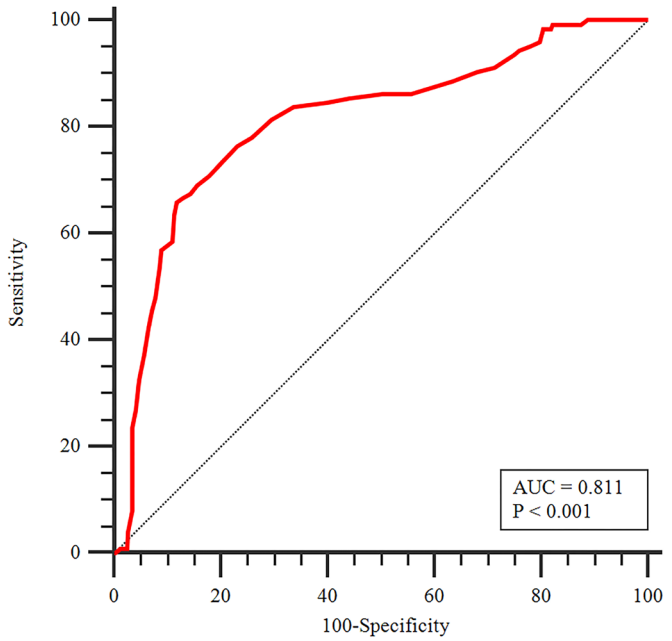
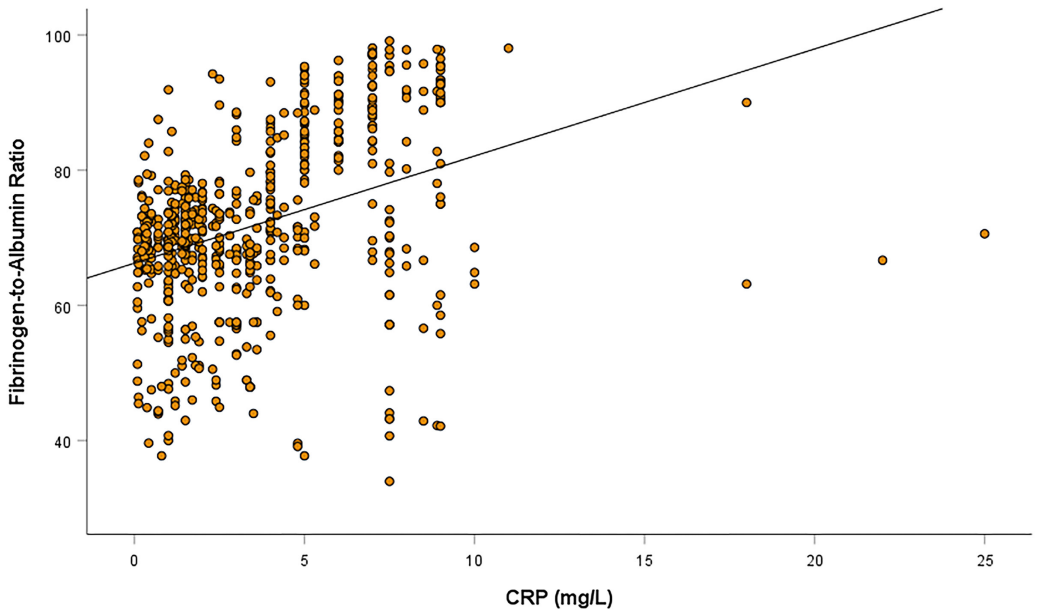


Figure 3. Correlation analysis of fibrinogen to albumin ratio with CRP level.



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RESEARCH

ASSESSMENT OF INAPPROPRIATE MEDICATION USE IN JORDANIAN ELDERLY HOSPITALIZED PATIENTS USING 2015 BEERS CRITERIA

Abstract

Introduction: Inappropriate prescribing in the elderly is associated with poor clinical outcomes. Using 2015 Beers criteria update, we aimed to evaluate the prevalence of inappropriate medication prescribing among elderly non-critically ill inpatients and to identify factors associated with inappropriate prescribing.

Materials and Method: This cross-sectional study included patients aged 65 years and over admitted to the internal medicine and surgical wards. Using 2015 Beers criteria, we assessed potentially inappropriate medication prescribing, both prior to admission and during the hospital stay. Binary logistic regression analysis was used to assess the predictors of PIM.

Results: Among 351 patients, the use of at least one PIM was identified in 29.3% of cases prior to admission, 98% of which continued to receive PIMs during the hospital stay. Additionally, at least one potentially inappropriate medication was identified in 47.2% of patients during the hospital stay. The most common PIMs prior to admission were proton pump inhibitors (26.2%), followed by alpha blockers (5.1%) and digoxin (4%). Proton pump inhibitors were also the most common PIMs in the hospital (42.5%), followed by alpha blockers (4.8%) and metoclopramide (4.3%).

According to the binary logistic regression analysis, factors that significantly affected PIM prescription in the hospital were the number of drugs prescribed in the hospital (odds ratio 1.222, P=0.001) and medical ward admission (odds ratio 1.686, P=0.035).

Conclusion: There is an alarmingly high prevalence of PIM use among Jordanian elderly patients, with polypharmacy being its major factor.

Keywords: Potentially inappropriate medication list; Aged; Prescription

ARAŞTIRMA

HASTANEDE YATAN ÜRDÜN'LÜ YAŞLI HASTALARDA 2015 BEERS KRİTERLERİ KULLANILARAK UYGUNSUZ İLAÇ KULLANIMININ DEĞERLENDİRİLMESİ

Öz

Giriş: Yaşlılarda uygunsuz reçeteleme ile kötü klinik sonuçlar arasında bir ilişki vardır. Bu çalışma güncellenen Beers 2015 kriterlerini kullanarak kritik olmayan yaşlı hastalar arasında uygunsuz ilaç kullanımının yaygınlığını değerlendirmeyi ve uygunsuz reçeteleme ile ilişkili faktörleri belirlemeyi amaçladı.

Gereç ve Yöntem: Bu kesitsel araştırmaya tıbbi ve cerrahi servislere yatırılan 65 yaş ve üzeri hastalar dahil edilmiştir. Beers 2015 kriterlerini kullanarak, hem hastaneye yatıştan önce hem de hastanesüreci sırasında, muhtemel uygunsuz ilaç reçetelemesini değerlendirdik. Muhtemel uygunsuz ilaç bağımsız değişkenlerini değerlendirmek için binary (ikili) lojistik regresyon analizi kullanılmıştır.

Bulgular: 351 hasta arasında, muhtemel uygunsuz olan en az bir ilacın kullanımı, hastaneye yatıştan önce vakaların % 29,3'ünde tespit edilmiş, bunların % 98 hastanede kalış sırasında muhtemel uygunsuz ilaçları almaya devam etmiştir. Hastane sürecinde hastaların % 47.2'sinde en az bir muhtemel uygunsuz ilaç tespit edildi. Hastaneye yatıştan önce en yaygın muhtemel uygunsuz ilaçlar proton pompası inhibitörleri idi (% 26.2), bunları alfa blokerler (% 5.1) ve digoksin (% 4) takip etmekteydi. Proton pompa inhibitörleri ayrıca hastane sürecinde verilen en sık muhtemel uygunsuz ilaçlardı (% 42,5), bunları alfa blokerleri (% 4,8) ve metoklopramid (% 4,3) takip etmekteydi.

Binary lojistik regresyon analizine göre, hastane sürecindeki muhtemel uygunsuz ilaçların reçetelenmesini önemli ölçüde etkileyen faktörler, hastanede reçetelenen ilaç sayısı (risk oranı 1,222, P = 0,001) ve tıbbi servisine tedavi görmeydi (risk oranı 1,686, P = 0,035).

Sonuç: Ürdünlü yaşlı hastalar arasında muhtemel uygunsuz ilaçlar kullanımı endişe verici derecede yüksek yaygınlıktadır. Muhtemel uygunsuz ilaçlar ile ilişkili ana faktör çoklu ilaç kullanımıdır

Anahtar sözcükler: Muhtemel uygunsuz ilaç listesi; Yaşlılar; Reçete

INTRODUCTION

Medication use in older adults is complex and challenging due to age-associated changes that include multiple morbidities, frailty, cognitive impairment, and other geriatric syndromes. Accordingly, the elderly often receive multiple medications and are at high risk of developing adverse effects (1).

Medications are considered to be potentially inappropriate for the elderly when the risk of harmful effects exceeds their potential benefit for the patient and when there is a safer, better tolerated, or more effective alternative (2).

There is an association between inappropriate prescribing in the elderly and mortality, need for additional healthcare services, adverse drug events, and decreased quality of life (3,4). Several studies were conducted to assess appropriate medication prescription among elderly in different settings including the community (5,6), primary care settings (7,8), nursing homes (9), and hospitals (10-13).

The 2015 Beers criteria (AGS) (14) encompass a list of potentially inappropriate medication (PIM) classes for use in the elderly. Previous research suggested that the Beers criteria could detect more PIMs than both the earlier version and the STOPP–START criteria (15).

To date, very few studies used 2015 AGS Beers criteria in the identification of PIMs among hospitalized patients (11-13).

The Study Objective

Using 2015 Beers criteria update, this study aimed to evaluate the prevalence of inappropriate medication prescribing among elderly non-critically ill inpatients and to identify factors associated with inappropriate prescribing.

MATERIALS AND METHOD

Study design and data collection

This cross-sectional study was conducted over 12 months between August 2016 and August 2017 at the Jordan University Hospital.

All consecutive patients aged 65 years and older admitted to the internal medicine and surgical wards were offered the opportunity to participate in the study. Critically ill patients were excluded. The study was compliant with the principles of the Declaration of Helsinki.

The study protocol was approved by the Jordan University Hospital Institutional Review Board.

The sample size calculation was conducted using OpenEpi software (Dean et al., 2013) (18). Based on the previous study by Gallagher et al. (2007) (5), the estimated study sample size should be 334 patients.

This study included a total of 351 patients, all of whom received detailed information about the study, including confidentiality and the anonymous nature of the data collected, before providing their consent to participation.

A clinical pharmacist performed data collection and determination of PIM by interviewing patients in addition to reviewing their medical records. In case of uncertainty of the PIM determination, a senior clinical pharmacist and an MD were consulted.

Study Instrument

Data collected during the interview included sociodemographic characteristics, the number of hospital admissions in the preceding year, and the pre-admission performance-based measure of independence in activities of daily living using the Katz Index (17). Self-rated health status was also assessed on a ten-point Likert-type scale with responses ranging from 1 (poor) to 10 (excellent). More data, including the length of hospital stay up to the day of data collection, specific diagnoses, and comorbidities quantified by the Charlson comorbidity index score, were collected from medical records (18). All drugs prescribed prior to hospital admission and during the hospital stay were also registered.

Determination of Potentially Inappropriate Medication (PIM)

PIMs were scanned using the 2015 "Beers Criteria for Potentially Inappropriate Medication Use in Older Adults" including prior-to-admission (PTA) medications and those prescribed during the hospital stay, and doses were assessed when necessary. In addition, medical records were reviewed to determine the reasons behind prescription and, subsequently, to reassess the appropriateness of each PIM.

Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 20. Univariate analysis was carried out using Chi-square test for categorical variables or an independent t-test for continuous variables to determine an association between the parameters studied and PIM prescription. A two-sided P-value<0.05 was considered to be statistically significant.

All variables found to have a significant association (P<0.05) with PIM prescription in the hospital by the bivariate analysis were entered into a binary logistic regression analysis to assess the predictors of PIM.

RESULTS

Three hundred and fifty-one patients were included, 51% of whom were males. The mean age was 73.7±5.8 years, the mean Charlson comorbidity index of study subjects was 5.4±1.6, and the mean Katz Index of Independence in Activities of Daily Living was 6.7±1.3 (Table 1). The mean number of prescribed drugs in the hospital was 8.1±3.8 (Table 2). The most common comorbidities were hypertension (74.4%), diabetes (58.7%), and chronic kidney disease (34.2%).

The use of at least one PIM was identified in 29.4% of elderly patients PTA, 98.1% of whom continued to receive PIMs during the hospital stay (Table 2). The most common inappropriately prescribed medications PTA were proton pump inhibitors (PPIs) (26.2%), followed by alpha blockers (5.1%) and digoxin (4%) (Table 3).

Table 1. Demographic characteristics of patients (N=351).

Gender, [N (%)]	
Male	179 (51.0)
Age (mean±SD) (min-max)	73.7 ±5.8 (65-94)
65-69	87 (24.8)
70-74	116 (33.0)
75-79	79 (22.5)
80-84	52 (14.8)
>85	17 (4.8)
Occupation [N (%)]	
Retired	168 (47.9)
Housewife	168 (47.9)
Employee	15 (4.3)
Educational level [N (%)]	278 (45.1%)
No formal education	219 (62.4)
Elementary school	38 (10.8)
Middle school	10 (2.8)
High school	23 (6.6)
Bachelor or higher degree	61 (17.4)
Smoking status [N (%)]	
Smoker	36 (10.3)
Nonsmoker	277 (78.9)
Ex-smoker	38 (10.8)

At least one PIM prescription during the hospital stay was received by 47.3% of patients.

Similar to prior to admission, PPIs were also the most common PIMs during the hospital stay

(42.5%), followed by alpha blockers (4.8%) and metoclopramide (4.3%) (Table 3).

As shown by the univariate analysis, PIM prescription PTA was associated with a higher total number of drugs, a higher Charlson comorbidity index (P<0.005 for both), admission to internal medicine ward (P<0.05), hypertension (P=0.044), ischemic heart disease (P=0.033), history of myocardial infarction (P=0.044), cerebrovascular disease (P=0.016), or diabetes mellitus (P=0.06) (Table 4).

Furthermore, during the hospital stay, PIM prescription was also associated with a higher total number of drugs both PTA and during the hospital stay (P<0.005 in each case) as well as with a higher Charlson comorbidity index (P=0.018), internal medicine ward admission (P<0.005), or cerebrovascular disease (P=0.02) (Table 4).

Binary logistic regression analysis revealed that the only variable that affected PIM prescription PTA was the total number of drugs received (OR 1.4, P<0.005).

Conversely, factors that significantly affected PIM prescription in the hospital were the number of drugs prescribed (OR 1.222, P=0.001) and admission to the medical ward (OR 1.686, P=0.035) (Table 5).

DISCUSSION

In this cross-sectional study conducted in Jordan using 2015 Beers criteria, we demonstrate a high prevalence of PIM use among elderly patients admitted to medical and surgical wards, both prior to admission and during the hospital stay.

The major study strength is that it is one of the first studies worldwide to assess the PIM prevalence among hospitalized elderly patients utilizing 2015 Beers criteria (11-13), the most updated prescribing assessment tool for elderly at the time of the study conduction. The criteria utilize evidence-based standards of the Institute of Medicine and its partnership with the AGS to update it regularly.

The changes in the 2015 AGS Beers criteria (14) from the previous 2012 version include the addition of two tables, one describing drug-drug interactions and the other illustrating medications that require dose reduction or avoidance in renal impairment. The 2015 AGS Beers list also contains five new medications or drug classes added.

Similar to our results of 29.3% receiving PIM PTA, 27.6% of community-dwelling elderly patients received at least one PIM in an Iranian study (19). In a Canadian study, a higher proportion (37%) of older people filled 1 or more inappropriate prescription (20). Notably, the above two studies used previous versions of Beers criteria. In the Canadian study, (20) a higher proportion of women (42.2%) than men (31.0%) filled potentially inappropriate prescriptions in the high-data coverage provinces, as opposed to our finding of lack of gender differences in PIM prescription. In a recently published study from Jordan, the prevalence of PIM in outpatients was much higher (62.5%) (21), probably due to the fact that the patients included in that study reside in rural area with less access to specialized medical care.

Our results show that, prior to admission, the most commonly prescribed PIMs were PPIs (26.2%). As this class of medications was not included in previous versions of Beers criteria, the most common PIM class in Iran was antihistamines (19), while in Canada benzodiazepines and other hypnotics, along with nitrofurantoin and estrogens in women, contributed the most to both frequency and cost of PIMs (20).

In this study, 47.2% of patients received at least one PIM prescription during the hospital stay. The PIM prevalence in our study was in agreement with the data from the US study (49% among elderly admitted with one or more of seven common medical diagnoses) (22), but lower than in a recent prospective cohort Italian study on hospital-discharged patients where the PIM prevalence was 63% (13). In a study from Brazil (23), the PIM prevalence was markedly higher (95.5%), probably due to the difference in inclusion criteria (the

authors defined elderly as individuals 60 years and above). In contrast, PIM prescription rates in our study were higher than those reported in Ireland (32%) (5), where generally acutely ill elderly patients were assessed using 2003 Beers criteria and patients received less number of medications (mean=5). Lower PIM prevalence was also reported among older emergency department patients in the United States (16.8%) (24).

Such marked variability in the prevalence of PIM prescription might be related to the difference in disease management guidelines and hospital drug formularies, study design (cross-sectional vs. retrospective cohort or prospective cohort), characteristics of the population groups (e.g., mean age, mean number of medications, generally in-hospital as opposed to critically ill patients), and the inclusion of PPI use duration for the first time in 2015 Beers criteria.

Notably, the most commonly prescribed PIM classes prior to hospital admission paralleled those in the hospital. Furthermore, the number of individuals with PIMs increased from 29.3% PTA to 47.2% during the hospital stay in our study, as compared with the increase only from 62.3% to 66.6% in a recent retrospective cohort study from Brazil (25).

Of importance, PPIs were again the most common PIMs during the hospital stay. De Oliviera et al. (2014) (21) also found that omeprazole, which at that time was not listed in the Beers criteria, was widely used in elderly patients. Moreover, the avoidance of PPI use beyond 8 weeks without justification was added to the 2015 Beers criteria. This was based on the evidence that supports an association between PPI exposure and Clostridium difficile infection, bone loss, and fractures (14). Among hospitalized Swiss patients in the internal medicine ward, PPIs were also prescribed frequently without clear indication, but the authors used STOPP criteria (26).

An important finding in our study was that all PIM prescribed PTA were continued at the hospital. This indicates that physicians at the hospital seldom review the medications that patients were receiving prior to admission.

As shown in our study, PIM prescription, both PTA and during the hospital stay, was more frequent in patients who received a higher total number of drugs. Earlier studies demonstrated an association between the total number of drugs received and PIM use, both in outpatient (3) and inpatient (5,24) settings. In a recent prospective cohort Italian study on hospital-discharged patients, the PIM prevalence was associated with psychiatric-behavioral disorders, the number of daily taken medications, and long-term care discharge, whereas better functional performance was protective (13).

Therefore, our study confirmed the earlier findings that polypharmacy is the major factor involved in PIM prescription for the elderly in both community and hospital settings. Overall, polypharmacy and inappropriate medication use are associated with adverse health outcomes, including mortality, hospitalization, falls, and cognitive impairment (4).

The association of PIM with admission to the internal medicine ward may be related to more complex medication regimens in patients receiving treatment in such ward as compared to surgical patients.

Some reports demonstrated improved pharmacotherapy outcomes for the elderly with proactive participation of pharmacists in performing systematic medication reviews and in actively educating other healthcare professionals such as physicians and nurses (13, 27). Further studies should be conducted to assess the impact of clinical pharmacist or clinical pharmacologist intervention on the PIM prevalence in different clinical settings.

Our study has some limitations:

1. Cross-sectional study nature does not allow to detect which factors associated with PIM are causal.

2. The Beers criteria were developed to assess PIM for the pharmaceutical products used in the USA. Thus, we might have underestimated the

frequency of PIM for products not in use in the USA or overestimated the frequency of those not in use in Jordan.

3. PTA medications were reported by patients during a structured interview, which might have resulted in recall bias.

4. The study sample might not be representative of Jordan since patients may receive relatively high-quality treatment in a teaching hospital. Thus, additional studies should be performed to address PIM prescription in other health sectors in Jordan.

5. The study did not investigate the association between PIMs and clinical outcome, e.g., actual adverse effects, including falls, in elderly patients. Further studies are needed to clarify the clinical impact of PIMs in the elderly population.

6. The assessment of PIMs was based only on one tool, Beers criteria. However, as mentioned above, the updated Beers list could detect more PIMs than older versions of Beers and STOPP–START tools.

CONCLUSIONS

There is an alarmingly high prevalence of PIM use among Jordanian elderly patients, with polypharmacy being its major factor.

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CONFLICT OF INTEREST

The authors declare that they do not have a conflict of interest.

Table 2. Clinical characteristics of patients (N=351).

Self-rated health status* [mean±SD] [min–max]	5.01±1.7
Length of hospital stay, days [mean±SD]	3.9±5.0
Reason of hospitalization [N (%)]	
Internal medicine admission Abdominal pain	201 (57.3) 17 (8.5)
Anemia	5 (2.5)
Neoplasia and chemotherapy	6 (3.0)
Cerebrovascular disease (transient ischemic attack or stroke)	8 (4.0)
Kidney disease (chronic kidney disease or acute kidney injury)	7 (3.5)
Cardiac causes (heart failure, acute coronary syndromes, arrhythmias)	25 (12.4)
Diabetes mellitus and its complications	6 (3.0)
Dyspnea (including chronic obstructive pulmonary disease exacerbation)	40 (19.9)
Acute infection (including urinary tract infection, pneumonia, cellulitis)	47 (23.4)
Others (e.g., dizziness, back pain, gastrointestinal bleeding, epistaxis)	40 (19.9)
Surgical ward admission	150 (42.7)

Orthopedic surgery	54 (36.0)
Urosurgery	16 (10.7)
Abdominal surgery	15 (10.0)
Diabetic foot ulcer (DFU)	20 (13.3)
Ophthalmic surgery	18 (12.0)
Others (e.g., thyroidectomy, open heart surgery, brain tumor surgery, varicose vein surgery)	27 (18.0)
Number of drugs received in the hospital [mean±SD]	**8.1±3.8**
Number of drugs received PTA [mean±SD]	**5.6±3.0**
Number of patients who were prescribed PIM PTA [N (%)]	
No PIM	248 (70.7)
One PIM	95 (27.1)
Two PIMs	8 (2.2)
Number of patients continuing inappropriate medications during the hospital stay [N (%)†]	**101 (98.1)**
Number of patients who were prescribed PIM during the hospital stay [N (%)]	
No PIM	185 (52.8)
One PIM	137 (39.0)
Two PIMs	24 (6.8)
Three or more PIMs	5 (1.4)
Number of patients with previously diagnosed comorbid conditions [N (%)]	
Hypertension	261 (74.4)
Atrial fibrillation	24 (6.9)
Coronary artery disease	92 (26.2)
Previous myocardial infarction	23 (6.6)
Congestive heart failure	34 (9.7)
Cerebrovascular disease	26 (7.4)
Chronic obstructive pulmonary disease	12 (3.40
Diabetes mellitus	206 (58.7)

*self-rated health status ranges from 1 (poor) to 10 (excellent)
†proportion of patients who continued in the hospital with the same PIM as prior to admission
‡Katz Index ranges from 7=high (patient independent) to 0=low (patient very dependent)
PIM, potentially inappropriate medication
PTA, prior to admission

Table 3. . Number of PIM identified by 2015 Beers criteria prior to admission and during the hospital stay.

Drug/drug class	N (%)*	
	Prior to admission	During the hospital stay
PIMs Anticholinergics	10 (2.8)	14 (4.0)
Alpha blockers†	18 (5.1)	17 (4.8)
Digoxin	14 (4.0)	14 (4.0)
Antipsychotics for behavioral and psychotic symptoms of dementia	1 (0.3)	1 (0.3)
TCA	-	2 (1.2)
Short-intermediate-acting benzodiazepines (Bromazepam) Long-acting benzodiazepines (chlordiazepoxide)	2 (0.6) -	2 (0.6) 2 (0.6)
Glyburide (glibenclamide)	7 (2.0)	6 (1.7)
Metoclopramide	-	15 (4.3)
PPIs‡	92 (26.2)	149 (42.5)
Meperidine	-	2 (0.6)
NSAIDs	-	w1 (0.3)
Drugs to be used with caution	19 (5.5)	19 (5.5)
Aspirin (as a primary prevention of cardiovascular disease in patients older than 80 years)	1 (0.3)	1 (0.3)
Isosorbide dinitrate	18 (5.2)	18 (5.2)
Drug interactions that should be avoided	0	0

*Valid percent

†Indicated for treatment of benign prostate hyperplasia, not as a routine treatment of hypertension

‡Appropriate prescription of PPI in medical ward patients include one of the following: treatment of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, erosive esophagitis, pathological hypersecretory conditions, prevention of NSAID- induced ulcer

PIM, potentially inappropriate medications

PPI, proton pump inhibitors

TCAs, tricyclic antidepressants

Table 4. Factors associated with PIM prescription.

Variables	PIM prescribed PTA			PIM prescribed in the hospital		
	Yes (N=103)	No (N=248)	P*	Yes (N=166)	No (N=185)	P*
Continuous	Mean ±SD			Mean ±SD		
Age	73.8±6.3	73.7±5.5	0.818	73.7±5.8	73.7±5.7	0.930
Number of drugs prescribed PTA	7.5±2.7	4.8±2.7	***<0.005***	6.5±3.0	4.8±2.7	***<0.005***
Number of drugs received in hospital				9.6±3.6	6.8±3.5	***<0.005***
Length of hospital stay, days				4.4±5.0	3.4±4.9	0.069
Charlson comorbidity index score	5.9±1.6	5.2±1.5	***<0.005***	5.6±1.6	5.2±1.5	***0.018***
Katz Index of Independence	6.7±1.2	6.6±1.4	0.542	6.7±1.3	6.7±1.3	0.954
Categorical variables	N (%)		P†	N (%)		P†
Gender						
Males	45 (43.6)	134 (54.0)	0.078	78 (47.0)	101 (54.6)	0.094
Females	58 (56.3)	114 (46.0)		88 (53.)	84 (45.4)	
Hospital ward						
Surgical ward				52 (31.3)	98 (53)	***<0.005***
Internal medicine				114 (68.7)	87 (47.0)	
Occupation						
Retired	42 (40.8)	126 (50.8)	0.231	71 (42.8)	97 (52.4)	0.095
Housewife	56 (54.4)	112 (45.2)		85 (51.2)	83 (44.9)	
Employee	5 (4.9)	10 (4.0)		10 (6.0)	5 (2.7)	
Occupation						
Hypertension	84 (81.6)	177 (71.4)	0.047	127 (76.5)	134 (72.4)	0.383
Atrial fibrillation	11 (10.7)	13 (5.2)	0.062	12 (7.2)	12 (6.5)	0.771
Ischemic heart disease	35 (34.0)	57 (23.0)	0.033	45 (27.1)	47 (25.4)	0.717
History of myocardial infarction	11 (10.7)	12 (4.8)	0.044	11 (6.6)	12 (6.5)	0.958
Congestive heart failure	14 (13.6)	20 (8.1)	0.114	21 (12.7)	13 (7.0)	0.078
Cerebrovascular disease	13 (12.6)	13 (5.2)	0.016	18 (10.8)	8 (4.3)	0.020
Diabetes mellitus	72 (69.9)	134 (54.0)	0.006	104 (62.7)	102 (55.1)	0.153
Chronic kidney disease	40 (38.8)	80 (32.2)	0.237	60 (36.1)	60 (32.4)	0.464

*calculated using independent-sample t-test, †calculated using Chi-square test
PIM – potentially inappropriate medication
PTA – prior to admission

Table 5. Results of logistic regression analysis for factors associated with PIM prescription in the hospital.

Variable	Ba	SE	P	OR	95% Confidence interval
Constant	1.488	0.680	0.029	0.226	-
Number of drugs prescribed PTA	0.027	0.071	0.711	0.974	0.847-1.120
Number of drugs prescribed in the hospital	-0.201	0.058	0.001*	1.222	1.091-1.372
Charlson comorbidity index	-0.038	0.080	0.963	1.038	0.887-1.215
Hospital ward (internal medicine)	-0.522	0.247	0.035*	1.686	1.038-2.7322
Cerebrovascular disease	0.648	0.460	0.159	0.523	0.212-1.289

aStandardized coefficient.

*Significant at P-value<0.05.

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RESEARCH

GERIATRIC BELL'S PALSY; RISK FACTORS AND LABORATORY RESULTS

Abstract

Introduction: Idiopathic facial paralysis or Bell's palsy is the most common type of peripheral facial paralysis. Advanced age and systemic diseases, such as diabetes and hypertension are considered as negative prognostic factors for Bell's palsy still controversial. Here, we aimed to compare the epidemiologic features and prognostic factors of patients with Bell's palsy aged ≥65 years.

Materials and Method: Records of patients with Bell's palsy (age, ≥65 years) who were admitted to our clinic between January 2008 and December 2017 were evaluated.

Results: We included 89 (72.4%) patients with Bell's palsy. The patients' ages varied between 65 and 91 (72.70 ± 5.9) years. Paralysis was in the right side in 59.6% (n = 53) and in the left side in 40.4% (n = 36) of the patients. Three (3.4%) patients had progressive facial paralysis. One (1.1%) had positive family history. After at least 6 months of follow-up, 71 (79.8%), 10 (11.2%), 6 (6.7%), and 2 (2.25%) patients were diagnosed with grade 1 and 2, 3, 4, and 5 Bell's palsy, respectively. Furthermore, a statistically significant correlation was observed between the initial paralysis grade and neutrophil-to-lymphocyte ratio (p=0.001).

Conclusion: Although old age is considered as a negative prognostic factor in patients with BP, we observed satisfactory recovery rates in geriatric patients who received appropriate treatment. In addition, a significant correlation was observed between the initial grade of facial paralysis and neutrophil-to-lymphocyte ratio upon admission, which can be considered as a prognostic factor.

Keywords: Bell palsy; Geriatrics; Inflammation; Neutrophils; Blood platelets; Prognosis

ARAŞTIRMA

GERİATRİK BELL PARALİZİSİ; RİSK FAKTÖRLERİ VE LABORATUVAR SONUÇLARI

Öz

Giriş: İdiopatik fasiyal paralizi ya da Bell paralizisi (BP) tüm yaş gruplarında görülebilen göreceli olarak sık bir durumdur. Farklı çalışmalarda ileri yaş, diyabet, hipertansiyon gibi eşlik eden sistemik hastalıklar BP'de kötü prognostik faktör olarak belirtilmesine rağmen bu konular hala tartışmalıdır. Bu çalışmamızda 65 yaş ve üstü BP tanısı almış hastalarda epidemiyolojik özellikler ve prognostik faktörler incelendi.

Gereç ve Yöntem: Ocak 2008-Aralık 2017 tarihleri arasında, paralizi sonrası en az 6. ay kontrolleri olan BP tanısı ile tedavi ve takip edilen altmış beş yaş ve üstü hastaların dosyaları retrospektif olarak tarandı.

Bulgular: Çalışmaya BP tanılı 89 hasta dahil edildi. Hastaların yaşları 65 ile 91 arasında (72.70±5.9) idi. Paralizilerin sağ tarafta görülme oranı % 59.6 (n=53); sol tarafta % 40.4 (n=36) idi. Üç (%3.4) olguda progresif fasiyal paralizi saptandı. Bir (%1.1) olguda aile anamnezi pozitifti. En az altı aylık takip sonunda 71 hasta (%79.8) evre 1-2, 10 hasta (%11.2) evre 3, 6 hasta (%6.7) evre 4, 2 hasta (%2.25) evre 5 olarak saptandı. Başvuru evresi yüksekliği ile Nötrofil Lenfosit Oranı (NLO) arasındaki ilişki anlamlı saptandı (p=0.001).

Sonuç: BP prognozunda ileri yaş negative bir prognostik faktör olarak kabul edilse de, uygun tedavi ile geriatrik hastalarda tatmin edici iyileşme oranları elde ettik. Ayrıca, prognostik faktör olarak değerlendirilebilecek olan NLO ile başvuru esnasındaki yüksek fasiyal sinir paralizisi derecesi arasında anlamlı bir korelasyon gözlendi.

Anahtar sözcükler: Bell paralizisi; Geriatri; İnflamasyon; Nötrofil; Trombosit; Prognoz

INTRODUCTION

The possible causes of facial nerve paralysis (FNP) include genetic predisposition and vascular ischemia as well as inflammation due to viral infections, autoimmune diseases, temporal bone fractures, head and neck tumors, and lesions of the central nervous system (1). Idiopathic facial paralysis, also known as Bell's palsy (BP), is the most common type of peripheral facial paralysis (PFP) (1). Peripheral facial nerve paralysis is typically self-limiting and presents with an acute onset with unknown causes. Moreover, peripheral facial nerve paralysis affects all muscle groups in just one side of the face (2). The clinical findings of BP usually vary according to the localization of the facial nerve lesion. BP can be observed in all age groups and is relatively common with a frequency of 20–30/100,000 people aged 15–45 years (3). Its incidence among men and women is equal, and 9% of all patients have a history of previous paralysis; approximately 0.3% of all patients have bilateral paralysis (3). Based on several studies, concomitant systemic diseases, such as diabetes and hypertension; advanced age; late-onset medical treatment; and discontinuation of drugs are still considered the negative prognostic factors of BP; however, still controversial (1-3). Besides, there are very few studies focused on geriatric patients, who we think require special attention, both for multiple conditions that may accompany due to advanced age and possible treatment difficulties (1-3).

Thus, we aimed to investigate the epidemiologic features, accompanying diseases, and treatment responses of geriatric patients with BP. We also analyzed the laboratory results to find out a possible prognostic factor among blood markers.

MATERIALS AND METHOD

We evaluated the records of patients aged over 65 years who received treatment for peripheral facial palsy in our clinic between January 2008 and December 2017, with a minimum follow-up period of 6 months. The institutional review board of our institution approved this retrospective study (approval no: 01/01.08.2018). Age, sex, duration from the onset to the treatment, previous history of facial palsy, accompanying diseases such as diabetes mellitus, hypertension, coronary heart disease and malignancies, associated symptoms, such as pain and skin eruption around the affected ear, hyperacusis, upper respiratory tract infection history, family history of facial paralysis, neurootologic examination and laboratory tests (Hemogram, serum biochemistry panel, serologic tests for Herpes Simplex Virus-1 (HSV) and Varicella Zoster Virus (VZV), radiologic tests such as cranial magnetic resonance and/or computer tomography, and treatment results of all patients were evaluated. Patients with paralysis were considered as BP if any specific cause could not be detected. During the first consultation and evaluation of treatment outcomes, the House–Brackmann (HB) facial nerve grading system was used to identify the degree of paralysis (4) (Table 1). In patients diagnosed with progressive facial paralysis, only the last grade of facial paralysis was taken into account.

At our clinic, the treatment of BP includes oral or intravenous methyl prednisolone (1 mg/kg/day) at tapered doses for 14 days. Further, antiviral therapy was included for the treatment of patients with positive serologic tests for HSV and VZV. Moreover, all the patients were assessed by an ophthalmologist for possible ophthalmic complications and a physical therapist for a suitable physical therapy program that includes facial muscle training. All patients underwent an initial blood test prior to treatment; and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), and fasting blood glucose (FBG, mg/dl) levels of all patients were examined. Radiographic imaging methods were used in patients who did not improve and/or progressed after 3 weeks.

Statistical Analysis

Descriptive statistics (arithmetic mean, median, minimum, maximum, standard deviation, and standard error) were first calculated on the basis

Table 1. House Brackman (HB) Facial Palsy Grading System.

Grade	Appearance	Forehead	Eye	Mouth
I	Normal	Normal	Normal	Normal
II	Slight weakness Normal resting tone	Moderate to good Movement	Complete closure Minimal effort	Slight asymmetry
III	Non-disfiguring weakness Normal resting tone	Slight to moderate Movement	Complete closure Maximal effort	Slight weakness Maximal effort
IV	Disfiguring weakness Normal resting tone	None	Incomplete closure	Asymmetric with Maximal effort
V	Minimal movement Asymmetric resting tone	None	Incomplete closure	Slight movement
VI	Asymmetric	None	None	None

of the obtained data. Spearman's rho correlation analysis, Kruskal–Wallis test, and Mann–Whitney U-test were performed in accordance with the data distribution. $p<0.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS, v.25.0) software was used for statistical analysis.

RESULTS

Of the total 123 patients with PFP who were aged≥65 years, 33 (27.6%) patients without BP were excluded. While paralysis was secondary to cerebrovascular disease in 12 (9.8%) of these patients, 8 (6.5%) were presented with Ramsey Hunt syndrome, 8 (6.5%) had chronic otitis media, 2 (1.6%) had malignant external otitis, 2 (1.6%) had temporal bone fracture secondary to trauma and 1 (0.8%) had temporal bone squamous cell carcinoma. The remaining 89 (72.4%) patients considered as BP were included in the study. The period from the onset of the disease to admittance to the hospital ranged from 1 to 7 (mean, 2.81 ± 1.89) days. Three (3.4%) patients were diagnosed with progressive facial paralysis. While one (1.1%) patient had a positive family history PFP, seven (7.8%) patients had a history of a recent upper respiratory tract infection. No recurrent and/or bilateral cases of facial paralysis were observed. The patients' ages ranged from 65 to 91 (mean, 72.70 ± 5.9) years. Of the patients, 48.3% (n = 43) were male and 51.7% (n = 46) were female. The average follow-up period ranged from 6 to 108 (mean, 41.31±26.07) months. Paralysis was observed on the right side in 59.6% of the patients (n = 53); while it was on the left side in 40.4% (n = 36) of them. Patients' initial paralysis grades were summarized in table 3.

At the end of at least 6 months of follow-up, 45 (50.6%), 26 (29.2%), 10 (11.2%), 6 (6.7%), and 2 (2.25%) patients presented with grade 1, 2, 3, 4, and 5 facial paralysis, respectively (Table 2). When facial paralysis was investigated in terms of seasonal distribution, 26 (29.2%), 24 (27%), 19 (21.3%), and 20 (22.5%) patients presented with paralysis during the spring, winter, summer, and fall months, respectively (Table 2). While 13 (14.6%) patients had diabetes mellitus (DM), 10 (11.2%) patients had hypertension (HT), 3 (3.4%) patients had coronary heart disease (CHD) 26 (29.2%) patients had DM, HT and CHD concomitantly, 8 (9%) patients had malignancies such as liver cirrhosis, acute lymphoblastic

Table 2. Patient characteristics.

	Frequency	Percent
gender		
woman	46	51.7
man	43	48.3
season		
winter	24	27.0
spring	26	29.2
summer	19	21.3
autumn	20	22.5
side		
right	53	59.6
left	36	40.4

leukemia, chronic lymphoblastic leukemia, laryngeal carcinoma, and bladder tumor; and 1 (1,1%) patients had chronic obstructive pulmonary disease, 2 patient (2,2%) of the had Alzheimer's disease, 1 patient (1,1%) had hypothyroidism. No systemic diseases were observed in the rest 25 (28.1%) of the patients (Table 3). When the correlation between the initial paralysis grade and the NLR, PLR, MPV, and FBG levels was assessed, a significant correlation was observed between the pre-treatment grade and NLR (p=0.00). Namely, as the grade increases, the NLR also increases. When treatment responses were evaluated, we found that, treatment response rates were higher in patients with advanced grade and high NLR ($p<0.05$). (Table 4)

No association was found between gender and pre-treatment ($p = 0.845$) and post-treatment grades ($p = 0.954$).

Cranial magnetic resonance examination of 44 patients who did not exhibit complete recovery after 3 weeks of treatment revealed no pathologic intracranial lesions or facial nerve pathologies.

Table 3. Clinical grades and accompanying diseases of the patients.

	Frequency	Percent
Gradepre (HB)		
2	14	15.7
3	31	34.8
4	23	25.8
5	18	20.2
6	3	3.4
Gradepost (HB)		
1	45	50.6
2	26	29.2
3	10	11.2
4	6	6.7
5	2	2.2
Accompanying diseases		
Dm	13	14.6
Ht	10	11.2
chd	3	3.4
hypothyroidism	1	1.1
copd	1	1.1
alzheimer	2	2.2
malignancy	8	9.0
dm+ht+cad	26	29.2
no disease	25	28.1

House Brackmann (HB), Diabetes Mellitus (DM), Hypertension (HT), Coronary Heart Disease (CHD), Chronic Obstructive Pulmonary Disease (COPD)

Table 4. . Correlation analysis results.

	r	p
Gradepre-NLR	0.392	0.001
Gradepre-PLR	0.045	0.672
Gradepre-MPV	0.07	0.512
Gradepre-FBG	-0.02	0.853
NLR-PLR	0.076	0.481
NLR-MPV	0.049	0.647
NLR-FBG	0.071	0.509
PLR-MPV	-0.001	0.995
PLR-FBG	-0.078	0.468
MPV-FBG	-0.085	0.427

Neutrophil to Lymphocyte ratio (NLR), Platelet to Lymphocyte ratio (PLR), Mean Platelet Volume (MPV), Fasting Blood Glucose (FBG, mg/dl)

DISCUSSION

BP is the most common cause of unilateral facial paralysis and accounts for 60%–70% of all FNP cases (5). Surgical treatment is generally recommended for cases where no regeneration is observed on electrophysiological tests or no clinical recovery (5). Hence, the prognosis of BP is extremely good, approximately 85% of all patients exhibit significant clinical recovery within 3-4 weeks (5). Previous studies have reported that 71% of all patients exhibit complete recovery of mimic muscle function, whereas 29% of the patients experience some kind of sequelae, such as fatigue, contraction, hemifacial spasm, or synkinesis of the facial muscles (5). Corticosteroids (CSs) are the most common agents used for the treatment of BP (6). Treatment with CSs, which is particularly initiated during the first week of disease onset, leads to muscle function recovery and reduces the complication rates (6). The use of antiviral agents is beneficial for the treatment of facial paralysis caused by HSV-1; however, its benefits for the treatment of BP are limited (6). CSs are recommended in the treatment of BP because they reduce edema and regenerate the facial nerve; further, CSs have motor function healing properties (6). The benefits of using CSs are supported by several randomized controlled studies (6). Treatment with CSs within the first 3 days of paralysis in patients with BP results in complete recovery of facial functions within 3–9 months as compared with placebos (6). A study reported that patients who received high doses of intravenous prednisolone and vitamins within the first 72 of the onset of paralysis had a better facial recovery rate compared with the control group who only received vitamins (7). Axelsson et al. (8) reported a considerable increase in the recovery rate when prednisolone treatment was initiated within 48 hours in patients aged >40 years. Moreover, Yeo et al. (9) reported that prednisolone treatment results in a high recovery rate in patients aged >60 years. Some studies also reported that HT, old age, and high degree of facial paralysis are the negative prognostic factors of BP and that 39% of the patients aged >60 years had HT (9,10). Moreover, when treatment is initiated within 72 hours of onset, the recovery rate is reportedly high in all age groups (10). Other studies have also reported that old age and comorbidities, such as DM, HT, CAD are negative prognostic factors for BP (11-13).

FNP related to HT may be caused by microhemorrhage in the facial nerve and vascular lesions (13,14). Moreover, DM also causes neuropathy (14). Although there is no proven correlation between DM and BP, some studies support the fact that the presence of DM is a possible etiologic factor of BP, which is found in 5%–20% of all patients (15,16). Inflammation and edema in a region where in the facial nerve passes through a narrow passage, such as the labyrinthine segment, stretch due to an impaired microvascular circulation related to DM and ischemic reasons are thought to be predisposing factors for paralysis (15,16). DM can also be a predisposing factor for PFP owing to the immunosuppressive effects of VZV (Ramsay Hunt syndrome) (16). Furthermore, it is more challenging to plan treatment with CS patients with DM (14-16). Bosco et al. (15) reported on DM for the first

time in 29 (19%) of 148 patients (age range, 47–65 years) with BP. In the present study, we identified DM, HT and/or CAD in 53 (59.5%) patients but these conditions did not alter our treatment plan since we hospitalized all of these patients with high risk for close monitorization.

Several studies concerning the relationship between BP and climate have shown that the incidence of BP increases during winter. Frequent and prolonged exposure to cold causes vasomotor changes in the facial region, thereby leading to reflex ischemia and edematous neuritis or reactivation of the HSV-1, which is in the latent state in the ganglion cells (17,18).

Progressive facial paralysis might be observed in some cases with BP. Kasse et al. (17) reported fulminant progressive facial paralysis rates between 27.5% and 72.5% among 1521 BP cases; they concluded that the progressive course is considerably correlated with a negative prognosis. In the current study, two (n=2.3%) patients presented with progressive facial paralysis. Both patients were presented with HB grade 3 and increased to grade 4 and 5, and they both had DM. After 6 months, one patient completely recovered, and the other regressed to grade 2.

Although the literature suggests the possibility of bilateral occurrence, we did not encounter such a case in our series. Most studies did not observe differences in terms of sex and side of the paralysis, as we found in our study (17-19).

Cha et al. (19) reported that 91.6% of the patients regressed to HB grade 1 and 2 at the end of 6 months. In the present study, approximately 80% of the patients regressed to grade 1 and 2. This relatively lower incidence may be attributed to the high incidence of accompanying risk factors among geriatric patients.

Several pathogens, such as the Epstein–Barr virus, cytomegalovirus, mumps virus, rubella virus, VZV, coxsackie virus, M. pneumoniae, and HSV-1 play roles in the etiology of PFP (20). Therefore, antiviral agents are frequently used to treat PFP. In the double-blind study conducted by Adour et al. (21), patients with BP were treated with acyclovir and prednisolone for 10 days. Compared with placebos and prednisone treatment, such treatments are considerably more effective in restoring facial muscle functions within 3 days of treatment onset. We identified HSV-1 DNA serology in 2 of the 7 patients with a history of upper respiratory tract infection. In patients with herpes simplex, acyclovir and standard steroids were administered for 10 days. Both patients had DM and were admitted with grade 3 and 4 paralysis. Complete recovery was observed in both patients at the end of 6 months.

Several recent studies have utilized the NLR and MPV as inflammation markers. Moreover, a high NLR was reported in studies involving patients with BP (22,23). Bucak et al. (22) reported that the NLR is considerably higher in patients with facial paralysis who did not recover even after the 1-year follow-up period compared to those who recovered. Kum et al. (23) reported a significant relationship between the grades of facial paralysis and NLR. In a similar study, Özler et al. (24) reported considerably high levels of NLR in patients who did not recover from facial paralysis within 3 months of treatment follow-up. Moreover, a correlation was found between the grades of facial paralysis and NLR upon admission. We observed significantly high rates of the NLR in patients with a high onset grade of facial paralysis ($p<0.01$); however, no significant correlation was observed between the MPV, TLR, and FBG levels and facial paralysis degree. We also found that higher NLR rates were associated with poor prognosis (Table 4.).

CONCLUSION

Although old age is considered a negative prognostic factor of prognosis in patients with BP, we observed satisfactory recovery rates in geriatric patients who received appropriate treatment. In addition, a significant correlation was observed between the grades of facial paralysis and NLR upon admission, and this can be considered a prognostic factor. Further multicenter studies with a larger sample size are warranted to confirm these results.

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RESEARCH

IMPACT OF SUBCLINICAL HYPOTHYROIDISM ON FREQUENCY OF PREMATURE VENTRICULAR CONTRACTIONS IN ELDERLY PATIENTS WITHOUT STRUCTURAL HEART DISEASE

Abstract

Introduction: Premature ventricular contractions (PVCs) are common arrhythmias, most of them requiring no follow-up or treatment. Subclinical hypothyroidism (SH) is defined as normal levels of free triiodothyronine (FT3) and free thyroxine (FT4), with elevation of serum thyroid stimulating hormone (TSH) levels (>4.2 mIU/l). We aimed to demonstrate the association of SH with the frequency of PVCs in elderly patients without structural heart disease.

Materials and Method: We included 327 consecutive elderly patients who underwent 24-hour Holter monitoring for the frequency of PVCs. The patients were initially divided into two groups with respect to the presence of SH. Later, the patients were divided into three groups with respect to the frequency of PVCs, with groups 1, 2 and 3 representing PVCs (<1,000/day), (1,000–5,000/day) and (>10,000/day), respectively.

Results: A total of 28 patients had SH. Number of PVCs was significantly higher in patients with SH (13104.7 ± 7007 vs 9286.7 ± 7724, p = 0.012) than in those without SH. On comparing the groups based on the frequency of PVCs, TSH levels were significantly higher in group 3 patients (>10,000 PVCs/day) than those in the others (p < 0.001). The percentage of patients with SH was significantly higher in group 3 (p = 0.005). According to univariate and multivariate analysis, SH was found to be an independent predictor of PVCs.

Conclusion: We found that SH is independently associated with frequent PVCs. We concluded that serum TSH concentration has a role in the frequency of PVC, therefore, SH may lead to a predisposition to ventricular arrhythmias.

Keywords: Hypothyroidism; Ventricular premature complexes; Electrocardiography ambulatory

ARAŞTIRMA

YAPISAL KALP HASTALIĞI OLMAYAN YAŞLI HASTALARDA SUBKLİNİK HİPOTİROİDİZMİN ERKEN VENTRİKÜLER KONTRAKSİYON SIKLIĞI ÜZERİNE ETKİSİ

Öz

Giriş: Prematür ventriküler kontraksiyonlar (PVK) sık görülür ve yapısal kalp hastalığı yokluğunda çoğu takip ve tedavi gerektirmez. Subklinik hipotroidi (SH), tiroid stimülan hormon yüksekliği (TSH>4.2 mIU/l) mevcutken serbest triiyodotironin(fT3) ve serbest tiroksin(fT4) düzeylerinin normal olduğu ve hipotirodizmin aşikar klinik bulgularının olmadığı durum olarak tanımlanır. Biz bu çalışmada yapısal kalp hastalığı olmayanlarda SH varlığının sık PVK ile ilişkili olup olmadığını araştırmayı amaçladık

Gereç ve Yöntem: Bu çalışmaya 24 saatlik holter monitorizasyonu (HM) ile PVK saptanan 327 geriatrik hasta dahil edildi. Öncelikle hastalar SH varlığına göre 2 gruba, sonrasında da PVK sıklığına göre 3 gruba ayrıldı. PVK sıkılığına göre sırasıyla grup 1 (<1000 PVK/gün), grup 2 (1000-5000 PVK/gün) ve grup 3 (>10000 PVK/gün) olarak tanımlandı.

Bulgular: Toplam 327 geriatrik hastanın 28'inde SH mevcuttu. SH olan hastalarda olmayanlara kıyasla PVK sayısı anlamlı olarak yüksek bulundu (13104.7±7007 vs. 9286.7±7724, p=0.012). PVK sıklığı ile yapılan gruplandırmaya göre, grup 3'te (>10000 PVK/gün) TSH düzeyleri anlamlı olarak yüksek bulundu (p<0.001) ve grup 3'te SH olan hasta yüzdesi diğer gruplara göre anlamlı olarak yüksekti (p=0.005). Tek ve çoklu değişkenli analiz sonuçlarına göre de SH sık PVK açısından öngördürücü olarak saptandı.

Sonuç: Biz bu çalışmada SH'nin PVK sıklığı ile bağımsız bir şekilde ilişkili olduğunu belirledik. Aynı zamanda TSH düzeyinin PVK sıklığında rolü olduğu, dolayısıyla SH'nin ventriküler aritmiler için öngördürücü olabileceği sonucuna vardık.

Anahtar sözcükler: Subklinik hipotroidi; Prematür ventriküler kontraksiyon; Holter monitorizasyonu

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INTRODUCTION

Premature ventricular contractions (PVCs) are common in the general population, and most of them are considered clinically insignificant in the absence of an underlying structural heart disease (1). Conversely, recent studies have shown that an increased risk of sudden cardiac death, myocardial infarction and all-cause mortality in patients with frequent PVCs, but with no structural heart disease (2). According to recent studies, it is now known that PVCs can cause impaired ventricular contractility, a larger left ventricle end diastolic diameter (LVEDD) and a larger left ventricle end systolic diameter (LVESD), known as the ventricular premature complex-induced cardiomyopathy. Additionally, PVCs without an underlying heart disease may be associated with ventricular tachycardia (VT), and an elimination of these PVCs with catheter ablation prevents further occurrence of VT (3).

Subclinical hypothyroidism (SH) is defined as normal free triiodothyronine (FT3) and free thyroxine (FT4) levels with an isolated elevation of serum thyroid stimulating hormone (TSH) levels, while the clinical findings of overt hypothyroidism are absent. The incidence of SH varies between 1% and 10% and increases with age (4). Hypothyroidism is associated with various cardiac pathologies, including impaired cardiac contractility, decreased cardiac output, increased systemic vascular resistance and cardiac electrical abnormalities (5). Electrocardiographic changes, including bradycardia, low voltage and varying degrees of heart block are commonly observed in hypothyroid patients. Hypothyroidism affects autonomic regulation of cardiovascular system and ventricular repolarisation. In some studies, QT prolongation and increased QT dispersion (QTd) have been shown to be directly related to TSH levels in overt hypothyroidism (6). These changes have been linked to the occurrence of malignant ventricular arrhythmias and sudden cardiac death (7). However, sustained or life-threatening ventricular ectopy is rarely seen in hypothyroid patients. Despite these findings in patients with hypothyroidism, there are very few studies that have evaluated the effects of SH on the cardiac electrophysiology (8,9). Although SH commonly occurs due to a thyroid hormone disorder, disagreement still exists about the necessity of treatment of this condition. Although some publications claim that patients with TSH > 10 mIU /l should be treated, there is no consensus on whether a treatment is necessary.

To the best of our knowledge, no previous study has analysed the impact of SH on PVCs. Therefore, in this study, we aimed to demonstrate whether the presence of SH is associated with the frequency of PVCs in geriatric patients without overt structural heart disease.

MATERIALS AND METHOD

Study Population

In the present study, we enrolled 327 consecutive elderly patients referred to our clinic for frequent PVCs, in excess of 1000/24 h on Holter monitoring (HM), and with no evidence of structural heart disease. Patients with a known cardiomyopathy, severe valvular heart disease, atrial fibrillation, serum electrolyte abnormalities, pacemaker or cardioverter defibrillator implantation were excluded from the study. The patients included in the study were divided into two groups based on the presence or absence of SH, and then, the same patients were divided into three groups with respect to the frequency of PVCs, as groups 1, 2 and 3 representing rare PVCs (<1,000 PVCs/day), moderate-frequency PVCs (1,000–5,000 PVCs/day) and frequent PVCs (>10,000 PVCs/day), respectively.

The baseline demographic and clinical characteristics were reviewed. The baseline laboratory findings including fasting plasma glucose, creatinine, potassium, haemoglobin (Hb), leukocytes, TSH, FT4, triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C) and total cholesterol levels were noted from the laboratory

recordings obtained prior to HM. SH was diagnosed by an elevated TSH value (>4.2mU/L) and FT4 values within the normal range. The patients with SH were not under any thyroid hormone replacement therapy. A standard 12-lead surface electrocardiogram (ECG) (25 mm/s and 10 mm = 1 mV) in the supine position was performed on each patient.

Echocardiography

Echocardiographic assessment was performed using a VIVID 7 Dimension Cardiovascular Ultrasound System (Vingmed-General Electric, Horten, Norway), with a 3.5 MHz transducer. Echocardiographic examination was performed in the left lateral decubitus position. Parasternal long- and short-axis views and apical views were used as the standard imaging windows. Ejection fraction (EF) was calculated by using modified Simpson's rule. All echocardiographic examinations were performed by an experienced cardiologist.

Holter monitoring and interpretation

Holter devices (Universal resting 12-lead Holter DMS 300-4A, MTM multitechmed gmbh, Schwarzwaldstrasse, Germany) were applied to the patients by our clinic's nurse; the patient came back after 24 hours and the nurse removed the device and uploaded the recordings to the Holter archive. Two cardiologists independently evaluated the recordings for PVCs, and the number of PVCs was recorded.

The study was approved by the Ethics Committee of Health Sciences University Ankara City Hospital.

Statistical analysis

Statistical analysis was performed using the SPSS 20.0 Statistical Package Program for Windows (SPSS, Inc., IL, USA). Continuous variables were presented as mean ± standard deviation and median with interquartile ranges, as appropriate, and the categorical variables as frequency and percentage. To test the normality of distribution, Kolmogorov–Smirnov test was used. A comparison between the two groups, according to the presence or absence of SH, was performed using the student's t-test. A comparison between the three groups, according to the number of PVCs, was performed using one-way ANOVA and Tukey's test for post-hoc analysis. Categorical variables were compared by χ^2 test. Multivariate logistic regression analysis, which included variables with $p < 0.1$, was performed to identify independent predictors of PVC frequency. The Pearson's correlation analysis was used to evaluate the relationship between the TSH levels and number of PVCs. A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 327 consecutive elderly patients who underwent 24-Hour HM for the frequency of PVCs were enrolled in our study. The clinical and baseline characteristics of the study population are shown in Table 1. The mean age of the study population was 73.7±3.8 years and 55.4% of the patients were females. SH was present in 28 patients of them. There were no differences between the two groups (defined according to the presence or absence of SH) with respect to age, gender, hypertension (HTN), diabetes mellitus (DM), medical treatments(ASA, β-blocker vs) and smoking status. Moreover, the baseline laboratory findings, except TSH and FT4, were not different between the two groups. Patients with SH had higher TSH levels (5.24 ± 1.2 vs. 2.26 ± 1.2, $p < 0.001$) than the patients without SH. ECG findings were similar regarding the baseline rhythm and heart rate with SH (88.6±13.0 vs. 84.4±15.3, p=0.160) and without SH ,respectively. None of the patients presented any sustained or non-sustained supra-ventricular tachyarrhythmias on 24-h ambulatory ECG monitoring. There were no differences between the 2 groups with respect to presence of premature atrial contractions with or without SH.(135.5±312 vs. 95.8± 206.3, p=0.356). Heart rate variability (HRV-SDNN24) on 24-h ambulatory ECG monitoring were similar between two groups (121.07±34.2 vs. 128.6± 30.1,

p=0.209).Number of PVCs was significantly higher in patients with SH (13104.7 ± 7007 vs. 9286.7 ± 7724, p = 0.012) than the patients without SH. None of the patients presented any sustained or non-sustained ventricular tachyarrhythmias on 24-h ambulatory ECG monitoring. Echocardiographic measurements, including EF, LVEDD, LVESD, IVSD,left atrial and systolic pulmonary artery pressure were similar between the two groups.

Table 2 demonstrates the characteristics of the study population with respect to the frequency of PVCs. There were no differences between the three groups with respect to gender, age, HTN, smoking status and family history of coronary artery disease. The EF was lower in group 3 than in group 1 and group 2 (p = 0.004). TSH levels were significantly higher in group 3 patients than those in group 2 and group 1 (3.10 ± 1.6 vs. 2.27 ± 1.2 and 2.07 ± 1.1, respectively, p < 0.001). The percentage of patients with SH was significantly different between all the three groups. While 14.8% of group 3 patients had SH, 7.1% and 2.8% (p = 0.005) of group 2 and group 1 patients, respectively, had SH.

According to univariate and multivariate analyses, SH (p = 0.003 / p = 0.005) was found to be predictive for frequent PVCs (Table 3).

In the correlation analysis, there was a moderate positive correlation between the TSH levels and number of PVCs in the patients (r = 0.482; p < 0.001) (Figure 1).

Table 1. Baseline characteristics of study patients according to the presence of subclinic hypothroidism (SH).

	SH – (n=299)	SH + (n=28)	P <0.001
Age, years	73.7±3.8	74.2±4.1	0.554
Gender, female n (%)	166(55.5)	15 (53.6)	0.843
Hypertension, n (%)	121(40.5)	9 (32.1)	0.389
Diabetes mellitus, n (%)	49(16.4)	4(14.3)	0.773
CAD, n (%)	31(10.4)	8(28.6)	0.005
Family CAD history, n (%)	10(3.4)	1(3.6)	0.957
Smoking, n (%)	28(9.5)	0(0)	0.089
Ejection fraction, %	58,7±5.2	59,3±4.6	0.522
LVEDD, mm	46.8±6.1	46.3±3.0	0.702
IVSD, mm	10.2±4.5	9.1±1.4	0.222
SPAP, mmhg	29.7±5.6	27.9±4.0	0.102
HR (bpm)	84.4±15.3	88.6±13.0	0.160

	SH – (n=299)	SH + (n=28)	P <0.001
PVCs	9286.7±7724	13104.7±7007	0.012
ASA, n (%)	69(23.1)	4(14.3)	0.285
β blocker, n (%)	209(69.9)	19(67.9)	0.822
ACEi, n (%)	62(20.7)	6(21.4)	0.931
ND-CCB, n (%)	71(23.7)	11(39.3)	0.70
Fpg, mg/dl	102.3±21.6	110.0±44.9	0.112
Creatinine, mg/dl	0.86±0.18	0.88±0.15	0.724
Hemoglobin, g/dl	14.1±5.3	13.7±1.1	0.741
Htc, %	42.7±3.6	42.4±3.6	0.705
Leukocyte, ×103 /ml	7.66±1.8	7.64±1.3	0.953
Platelet, $\times 10^3$ /ml	242±55	244±68	0.804
Ldl-c, mg/dl	112±32	110±20	0.674
Hdl-c, mg/dl	50±12.7	47±9.2	0.170
Triglyceride, mg/dl	158±69.4	177±90.2	0.171
Tsh, uı/ml	2.26±1.2	5.24±1.2	<0.001
fT4, UI/mL	1.16±0.4	1.00±0.1	0.037
Group 1, n (%)	103(34.7)	3(2.8)	0.010
Group 2, n (%)	92(30.8)	7(7.1)	0.525
Group 3, n (%)	104(34.8)	18(14.8)	0.002

Data are presented mean ± SD or n (%).

CAD- coronary artery disease; ASA - asetil salicylic acite; ND-CCB – nondihydropyridine calcium channel-blocking agent; FPG- fasting plasma glucose; HDL-C- high-density lipoprotein cholesterol; LAD- left atrium diameter; LDL-C- low-density lipoprotein cholesterol; LVEDD- left ventricle end-diastolic diameter; IVSD - interventricular septum end-diastolic

diameter;SPAP: systolic pulmonary artery pressure; PVC- premature ventricular contraction; fT4- free level of thyroxine; TSH- thyroid-stimulating hormone

Table 2. Patient characteristics according to PVC frequency.

	Group 1 (n=106) (PVC 1000 5000/day	Group 2 (n=99) (PVC 5000-10000 day)	Group 3 (n= 122) (PVC> 10000 day)	P
Age, years	74.2±4.1	73.2 ±3.4	73.8±3.9	0.151
Gender, female n (%)	73(40.3)	64(35.4)	44(24.3)	<0.001
Hypertension, n (%)	44(41.5)	36(36.4)	50(41.0)	0.709
Diabetes mellitus, n (%)	12(22.6)	4(7.5)	37(69.8)	<0.001
CAD, n (%)	5(12.8)	10(25.6)	24(61.5)	0.002
Family CAD history, n (%)	5(44.5)	0(0)	6(54.5)	0.081
Smoking, n (%)	6(21.4)	11(39.3)	11(39.3)	0.378
SH, n (%)	3(2.8)	7(7.1)	18(14.8)	0.005
Ejection fraction, %	59.6±5.4	59.2±5.5	57.5±4.3	0.004
LVEDD, mm	46.4±3.4	48.5±3.6	45.5±8.3	0.001
LAD, mm	36.8±4.7	38.5±3.3	36.6±3.0	< 0.001
SPAP, mmhg	28.8±5.8	29.9±6.4	29.9±4.4	0.298
FPG, mg/dL	97.9±19.5	98.3±13.8	111±31.9	<0.001
Creatinine, mg/dL	0.87±0.2	0.84±0.1	0.88±0.1	0.220
Hemoglobin, g/dL	14.3±8.8	13.9±1.2	13.9±1.5	0.772
Htc, %	41.8±3.2	42.8±3.3	43.3±3.9	0.009
Platelet, $\times 10^3$ /mL	244±52	237±51	237±63	0.580
Leukocyte, $\times 10^3$ /mL	7.6±2.0	7.6±1.5	7.6±1.7	0.951
LDL-C, mg/dL	113±31	104±31	117±29	0.008
HDL-C, mg/dL	52±15	44±9	52±10	<0.001
Triglyceride, mg/dL	136±66	162±61	177±78	<0.001
TSH, UI/mL	2.07±1.1	2.27±1.2	3.10±1.6	< 0.001
fT4 ,mg/dl	1.07±0.29	1.18±0.28	1.19±0.54	0.075

Data are presented mean ± SD or n (%).

CAD- coronary artery disease; FPG- fasting plasma glucose; Htc-Hematocrit; HDL-C- high-density lipoprotein cholesterol; LAD- left atrium diameter; LDL-C- low-density lipoprotein cholesterol; LVEDD- left ventricle end-diastolic diameter; SH – Subclinical hypothyroidism SPAP- systolic pulmonary artery pressure; PVC- premature ventricular contraction; fT4- free level of thyroxine; TSH- thyroid-stimulating hormone

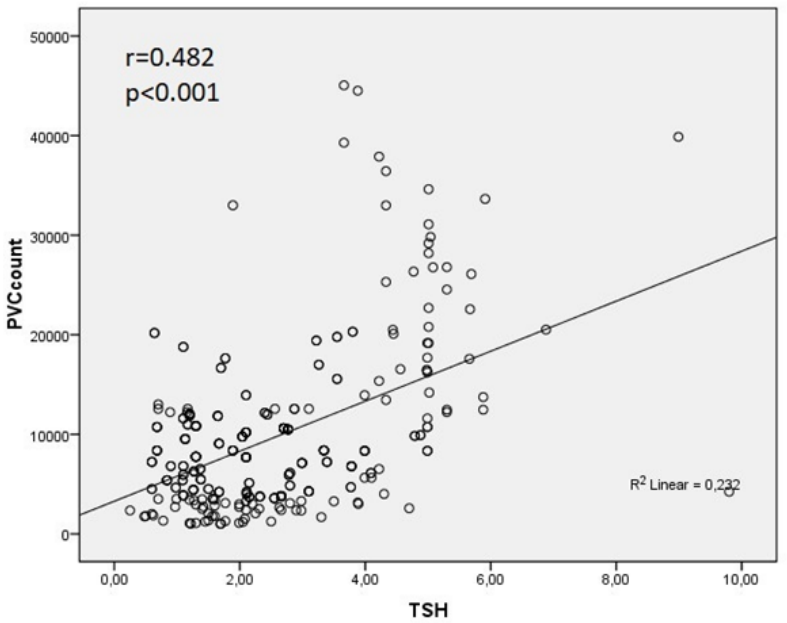
Table 3. Univariate and multivariate analyses for predictors of frequent premature ventricular contraction

Variable	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p value	OR	95 % CI	p value
Age	1.001	0.945-1.061	0.962			
Hypertension	1.085	0.687-1.714	0.726			
Diabetes mellitus	5.142	2.712-9.750	<0.001	4.017	1.975-8.253	<0.001
Family CAD history	2.095	0.625-7.017	0.231			
Smoking	1.110	0.502-2.457	0.797			
CAD	3.086	1.548-6.150	0.001	2.613	1.227-5.510	0.013
Ejection fraction	0.930	0.888-0.973	0.002	0.960	0.912-1.010	0.117
LVEDD	0.943	0.899-0.988	0.014			
LAD	0.932	0.876-0.990	0.023			
FPG	1.026	1.014-1.037	<0.001			
Creatinine	1.790	0.515-6.217	0.359			
Hemoglobin	0.992	0.944-1.043	0.753			
Platelet	1.001	0.997-1.005	0.651			
Leukocyte	0.980	0.864-1.111	0.751			
LDL-C	1.009	1.001-1.016	0.022			
HDL-C	1.024	1.005-1.043	0.011			
Triglyceride	1.006	1.002-1.009	0.001	1.004	1.000-1.007	0.044
TSH	1.572	1.326-1.862	<0.001			
fT4	1.443	0.838-2.484	0.186			
SH	3.375	1.503-7.578	0.003	3.469	1.461-8.241	0.005

Bolded values indicate statistically significant odds ratio.

CI: confidence interval; OR: odds ratio; CAD- coronary artery disease; FPG- fasting plasma glucose; HDL-C- high-density lipoprotein cholesterol; LAD- left atrium diameter; LDL-C- low-density lipoprotein cholesterol; LVEDD- left ventricle end-diastolic diameter; SH – Subclinical hypothyroidism; fT4- free level of thyroxine; TSH- thyroid-stimulating hormone

Figure 1. Correlation between PVC count and TSH.



DISCUSSION

Two major findings of our study were as follows: (1) SH was independently associated with frequent PVCs, and (2) there was a moderate positive correlation between the TSH levels and number of PVCs in the patients. To our knowledge, this is the first study defining the relationship between frequent ventricular PVCs and SH in patients with structurally normal hearts.

PVCs are frequently seen in healthy population with increasing age. In patients without structural heart disease, this is regarded as benign by many physicians. However, studies in the last 15 years have showed their potential pathogenicity (10). PVCs can lead to impaired ventricular contractility and dilation of the ventricular size, known as PVC-induced cardiomyopathy. Previous studies have suggested that there is a correlation between the PVC load and left ventricular function, and a higher PVC load is associated with a lower left ventricular EF, a larger LVEDD and a larger LVESD (11). Other studies have shown improvement in left ventricular systolic function after suppression of PVCs in patients with dilated cardiomyopathy (11-13). PVCs are commonly associated with various cardiac conditions like myocardial ischaemia and heart failure, but can also be seen in non-cardiac conditions such as pulmonary disease, consumption of alcohol, caffeine, β-agonists, cocaine or amphetamines.

The effects of thyroid hormone deficiency on the heart are well known. An elevated TSH level can adversely affect the cardiovascular system (14). Previous studies have shown that overt hypothyroidism is characterised with the prolongation of QTd and increased sympathetic influence. Inukai et al. showed that hypothyroidism was associated with increased sympathetic activity of the heart (15). Cacciatori et al. suggested that thyroid hormone deficiency was associated with an increased sympathetic influence on the autonomic cardiovascular system. Some studies demonstrated that SH increased the cardiovascular risk factors,

including altered lipid profile, impaired cardiac contractility, decreased cardiac output, increased systemic vascular resistance and cardiac electrical abnormalities (16-18). Galetta et al. showed that the patients with SH had a higher QTd and lower heart rate variability (HRV) measurements compared with the healthy control group, and that the QTd was positively associated with TSH value, with the measurements returning to normal after treatment (9). In general, increased QTd has been shown to be associated with increased risk of malignant ventricular tachyarrhythmia and sudden cardiac death (7). Çelik et al. proved that HRV and heart rate (HR) turbulence was reduced in the patient group, and the cardiac autonomic functions did not improve effectively with levothyroxine treatment (7,19). In a previous study by Mahajan et al., it was also demonstrated that autonomic dysfunction may be seen in both subclinical and frank hypothyroidism (5).

The mechanism of autonomic dysfunction in hypothyroidism is thought to be because of increased adrenalin levels associated with a receptor or post-receptor sensitivity, decreased chronotropic response to beta-adrenergic stimulation and an increase in thyrotropin-releasing hormone, which has a direct effect on the sympathetic activity (20). The thyroid hormones can also have direct effect on the heart, which includes increased protein deposition in the extracellular space, leading to accumulation of water in the myocardial wall. The resulting myocardial oedema may lead to fibrosis and regional homogeneity disorder in ventricular repolarisation (20,21). Bakiner et al. showed that QT and the corrected QT (QTc) intervals were prolonged in patients with SH and that the return of serum TSH levels to the values within the normal range resulted in normalisation of QTc (8). A recent study showed that SH may change the autonomic modulation of HR and cause heterogeneity of ventricular healing times (9). These differences may contribute to the prevalence of increased ventricular arrhythmias, as a result of more heterogeneous ventricular repolarisation in patients with SH. It is widely accepted that autonomic control plays an important role in the genesis, maintenance and interruption of ventricular arrhythmia (VA) (22). In most cases, VAs are evoked or aggravated by sympathetic activation and/or decreased vagal tone, despite the heart being structurally normal or abnormal. In addition, a considerable part of idiopathic PVCs is sensitive to beta-blockers in clinical practice. Suggested physiological mechanisms for PVCs include enhanced automaticity, re-entry and triggered activity. Sympathetic activation can enhance the automaticity in ectopic focus and induce the cAMP-mediated triggered activity, which might explain its facilitating effects on idiopathic PVCs (23).

In this study, we showed that the SH was associated with frequent PVCs. This result, as mentioned in older studies, may be related to the effects of SH on cardiac autonomic activity (increased sympathetic activity, decreased vagal tonus) and the effects on electrocardiographic repolarisation parameters. Thus, we suggest that SH, with increased sympathetic activity in the background, may cause frequent PVCs, but further studies are required to determine the relation between the frequency of PVC in patients with SH. Our study also showed that patients with frequent PVCs had lower EF values. Similar to previous studies, we have found that PVCs that are commonly seen in patients with apparently normal hearts are associated with reduced EF compared with the patients without frequent PVCs. However, as opposed to previous studies, the LVEDD values were not found to be higher in patients with frequent PVCs. Although the TSH level that dictates a need for treatment in patients with SH is controversial, it has been reported that the repolarisation anomaly in patients with SH can be corrected by treatment with L-thyroxine, and this condition is particularly evident in patients with TSH > 10mIU/l (8,9,24). Since there is no study evaluating the relationship between SH and the frequency of PVCs, further researches are required to recommend this treatment to the patients.

This study should be interpreted within several limitations. First, this was a retrospective

observational study. Without any intervention and a prospective design, it was not possible to illustrate the direct effect of SH on the frequency of PVCs. The direct relationship between the PVCs, SH and clinical outcome should be evaluated in prospective large-scale studies, with a longer follow-up period. Secondly, the PVC classification was dependent on a single 24-h HM, which is liable to higher variability and lesser clear classification, in comparison with a longer monitoring time.

In summary, our study showed that SH was significantly and independently associated with frequent PVCs. Furthermore, we found that there is a positive correlation between the TSH levels and number of PVCs. Further studies are needed to find out the relation between the frequency of PVCs and the SH.

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CONFLICT OF INTEREST

The author declares that they have no conflicts of interest to declare.

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RESEARCH

DETERMINATION OF POLYPHARMACY AND INAPPROPRIATE DRUG USE IN PATIENTS AGED OVER 65 YEARS WHO PRESENTED TO THE EMERGENCY DEPARTMENT

Abstract

Introduction: No study in the literature has reported the rate of inappropriate drug use among older patients admitted to emergency department in Turkey. This study aimed to evaluate polypharmacy and inappropriate drug use by elderly patients admitted to the emergency department.

Materials and Method: Patients aged ≥65 years were prospectively assessed for appropriateness of drugs they use between March and May 2016 according to both the 2012 Beers Criteria and STOPP Version 2 Criteria. Inappropriate drug use was separately assessed according to these criteria, and both patient and drug counts were calculated to assess inappropriate drug use in the study population. Age, gender, date of admission to the emergency department, blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation, state of consciousness, additional diseases, number of drugs used, names of drugs used, clinical outcome were recorded.

Results: Among 835 study participants, 406 (48.6%) were females and 429 (51.4%) were males. Mean age was 74.2 ± 6.6 years. The rate of polypharmacy and excessive polypharmacy was the highest in patients diagnosed with hypertension (35.0% and 16.0%, respectively) and lowest in patients diagnosed with chronic renal failure (2.0% and 2.0%, respectively). In total, 835 patients were using 5 637 drugs. Inappropriate drug use was present in 431 (51.6%) patients according to the STOPP Version 2 Criteria and in 441 (52.8%) according to the 2012 Beers Criteria.

Conclusion: Emphasis on inappropriate drug use will help physicians in the emergency department and other healthcare professionals reduce side effects and complications of medications and reduce emergency admissions to hospital.

Keywords: Inappropriate drug use; Potentially inappropriate medication list; Aged

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ARAŞTIRMA

ACİL SERVİSE BAŞVURAN 65 YAŞ ÜZERİ HASTALARDA POLİFARMASİ VE UYGUNSUZ İLAÇ KULLANIMININ BELİRLENMESİ

Öz

Giriş: Türkiye'de acil servise başvuran yaşlı hastalarda literatürde herhangi bir uygunsuz ilaç kullanımı oranı bildirilmemiştir. Bu çalışma, acil servise başvuran yaşlı hastaların çoklu ilaç kullanımını ve uygun olmayan ilaç kullanımını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: 65 yaşın üstündeki hastalar, 2012 Beers Kriterleri ve Yaşlı Kişilerin Potansiyel Olarak Uygun Olmayan Reçetelerinin Tarama Aracı Sürüm 2 Kriterlerine göre Mart ve Mayıs 2016 arasında kullandıkları ilaçların uygunluğu açısından prospektif olarak değerlendirildi. Uygun olmayan ilaç kullanımı, bu kriterlere göre ayrı ayrı değerlendirildi ve hem hasta hem de ilaç sayıları, çalışma popülasyonunda ki uygunsuz ilaç kullanımını değerlendirmek için hesaplandı.Yaş, cinsiyet, acil servise geliş tarihi, kan basıncı, nabız, solunum sayısı, vücut sıcaklığı, oksijen saturasyonu, bilinç durumu, ek hastalıklar, kullandığı ilaçlar ve isimleri ve klinik sonuçlanma kaydedildi.

Bulgular: 835 katılımcının 406'sı (% 49) kadın, 429\'u (% 51) erkekti. Yaş ortalaması 74.18 ± 6.58 yıldı Polifarmasi ve aşırı polifarmasi oranı, hipertansiyon tanısı alan hastalarda (sırasıyla% 35 ve % 16) en yüksek, kronik böbrek yetmezliği tanısı alan hastalarda en düşüktü (sırasıyla% 2 ve% 2). Toplamda 835 hasta 5.637 ilaç kullanıyordu.Yaşlı Kişilerin Potansiyel Olarak Uygun Olmayan Reçetelerinin Tarama Aracı Versiyon 2 Kriterlerine göre 431 (% 51.6) hastada uygunsuz ilaç kullanımı ve 2012 Beers kriterine göre 442 kişide (% 52.9) uygunsuz ilaç kullanımı mevcuttu.

Sonuç: Uygunsuz ilaç kullanımına önem verilmesi, acil servisteki hekimlerin ve diğer sağlık çalışanlarının ilaçların yan etkilerini ve komplikasyonlarını azaltmasına ve hastaneye acilen kabulü azaltmasına yardımcı olacaktır.

Anahtar sözcükler: Uygunsuz ilaç kullanımı; Potansiyel uygunsuz reçete; Yaşlılık

INTRODUCTION

In recent years, the awareness of potential risks of inappropriate drug use has increased along with polypharmacy (multiple drug use) in the older population (age, >65 years). Polypharmacy is a risk factor that is likely to cause undesirable consequences, such as hospitalization and falls, as older people are more vulnerable to drug–drug interaction, side effects, and dosing errors (1).

Although defined and classified in different ways in different resources, polypharmacy generally refers to the use of 5–10 drugs by a patient. Use of >10 drugs is defined as excessive polypharmacy (2). In older individuals, polypharmacy is quite common given that they are diagnosed with multiple diseases. In this group, polypharmacy makes treatment more complicated and increases length of hospitalization and costs (3). Approximately 30.0% of hospitalization results from problems related to drug use (4). Furthermore, older patients are more susceptible to side effects of drugs and thus cannot use every drug. Studies mostly refer to the 2012 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults to evaluate the appropriateness of medication (5). Prescribing appropriate medications to older patients reduces side effects (6). The aim of this study is to determine the rate of inappropriate drug use in older patients who were admitted to our emergency department and to make recommendations to reduce inappropriate drug use.

MATERIALS AND METHOD

After approval was obtained from the local Ethics Committee, this study was conducted in the Emergency Department of Eskisehir Osmangazi University Hospital between March and May 2016 based upon a prospective and observational research design. Patients aged ≥65 years were included in the study. The exclusion criteria for participation in the study were age of <65 years and not providing informed consent for participation. The following information was noted on the observation form for each patient: age, gender, date of admission to the emergency department, blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation, state of consciousness, additional diseases, number of drugs used, names of drugs used, clinical outcome after the provision of medical care (discharge, hospitalization (in the intensive care unit or related medical department), refusal of treatment, transfer to another healthcare center, death, and leaving the hospital against medical advice).

Drugs Used and Appropriateness According to the 2012 Beers and STOPP Version 2 Criteria

For the purpose of this study, statistical analyses were performed based on the following parameters:

- The appropriateness of drugs according to the 2012 Beers and STOPP Version 2 Criteria
- The number of inappropriate drugs
- Falls caused by inappropriate drugs, according to the 2012 Beers Criteria
- The organ system affected by inappropriate drugs, according to the STOPP Version 2 Criteria

Statistical Method

IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. was used to perform statistical analyses. Categorical variables were presented as numbers (n) and percentages (%). Continuous data are given as a mean ± standard deviation.

RESULTS

The study was conducted with 835 patients: 406 (48.6%) females and 429 (51.4%) males. The participants' mean age was 74.2 ± 6.5 years. The distribution of comorbidities in the participants is presented in Figure 1. The relationship between

comorbidities and number of drugs is provided in Table 1. Overall, 835 patients were using a total of 5,637 drugs. The average number of drugs used was 6.8 ± 3.2. The distribution of patients by the number of drugs used is presented in Table 2.

According to the STOPP Version 2 Criteria, the number of inappropriate drugs used was 688 in total and the number of patients using inappropriate drugs was 431 (51.6%). The number of inappropriate drugs used was one drug in 241 (28.9%) patients, two in 137 (16.4%), three in 41 (4.9%), four in 10 (1.2%), and five in two (0.2%) (Table 3). According to the 2012 Beers Criteria, the number of inappropriate drugs used by participants was 843 and the number of patients using inappropriate drugs was 442 (52.9%). The number of inappropriate drugs was one drug in 205 (24.6%) patients, two in 133 (15.9%), three in 58 (6.9%), four in 33 (4.0%), five in 12 (1.4%), and six in one (0.1%) (Table 3).

Profiles of Inappropriate Drugs

According to the 2012 Beers Criteria, the most commonly used inappropriate drugs are SSRIs (122 patients, 14.6%), strong anticholinergics (97, 11.6%), NSAIDs (86, 10.3%), and aspirin (58, 6.9%). According to the STOPP Version 2 Criteria, the most common violations were related to the category of duplication (165 patients, 19.8%), cardiovascular system (107, 12.8%), use of antiplatelet drugs (103, 12.3%), and central nervous system (87, 10.4%). According to the STOPP Version 2 Criteria, the most frequently duplicated drugs were NSAIDs (66 patients, 40.0%), steroids for respiratory disorders (23, 14.0%), proton-pump inhibitors (18, 11.0%), thiazide diuretics (18, 11.0%), ASA (13, 8.0%), and paracetamol (13, 8.0%).

Table 3. Univariate and multivariate analyses for predictors of frequent premature ventricular contraction

Comorbidities		Number of drugs				Total
		0	1–5	6–9	>9	
DM	No	14 (2.0%)	255 (31.0%)	262 (31.0%)	79 (9.0%)	610 (73.0%)
	Yes	1 (0.1%)	46 (6.0%)	107 (13.0%)	71 (9.0%)	225 (27.0%)
HT	No	14 (2.0%)	149 (18.0%)	78 (9.0%)	13 (2.0%)	254 (39.0%)
	Yes	1 (0.1%)	152 (18.0%)	291 (35.0%)	137 (16.0%)	581 (70.0%)
COPD	No	15 (2.0%)	276 (33.0%)	276 (33.0%)	91 (11.0%)	658 (79.0%)
	Yes	0 (0.1%)	25 (3.0%)	93 (11.0%)	59 (7.0%)	177 (21.0%)
CRF	No	15 (2.0%)	289 (35.0%)	350 (42.0%)	133 (16.0%)	787 (94.0%)
	Yes	0 (0.1%)	12 (1.0%)	19 (2.0%)	17 (2.0%)	48 (6.0%)
CHF	No	15 (2.0%)	294 (35.0%)	325 (39.0%)	98 (12.0%)	732 (88.0%)
	Yes	0 (0.1%)	7 (1.0%)	44 (5.0%)	52 (6.0%)	103 (12.0%)
CAD	No	15 (2.0%)	251 (30.0%)	183 (22.0%)	37 (4.0%)	486 (58.0%)
		0 (0.1%)	50 (6.0%)	186 (22.0%)	113 (14.0%)	349 (42.0%)
Others	No	15 (2.0%)	70 (8.0%)	37 (4.0%)	11 (1.0%)	133 (16.0%)
	Yes	0 (0.1%)	231 (28.0%)	332 (40.0%)	139 (17.0%)	702 (84.0%)

DM, diabetes Mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CHF, congestive heart failure; CAD, coronary artery disease

The use of anticholinergics in patients admitted to the emergency department after a fall was investigated, and seven of 35 patients were found to be inappropriately using anticholinergics according to the 2012 Beers Criteria and five were inappropriately using anticholinergics according to the STOPP Version 2 Criteria.

Table 2. Distribution of the number of drugs among patient.

Number	Number of patients	Percentage (%)
0	15	1.8
1–5	301	36.0
6–9	369	44.2
>9	150	18.0
Total	835	100.0

DISCUSSION

The participants' mean age was 74.2 ± 6.6 years. Given that life expectancy is 79.4 years in females and 73.7 years in males according to 2015 data, the older population provides an important source of information in Turkey.

The population census of Turkey in 2015 showed that the number of people aged ≥65 years was 6 495 239 (8.2% of the total population). There is limited information in the literature particularly with regard to the elderly. Because of the aging of the population in Turkey and lack of sufficient information in the literature, this study potentially provides a significant source of information for the treatment of older individuals.

This study has focused on inappropriate drug use in the elderly based on the STOPP Version 2 Criteria and 2012 Beers Criteria. Given that the number of similar studies is limited in the literature, the present study may play a guiding role in research.

Increase in the aging population has affected the entire healthcare system, particularly the

Table 3. Univariate and multivariate analyses for predictors of frequent premature ventricular contraction.

Number of Inappropriate drug use	2012 Beers Criteria		STOPP Version 2 Criteria	
	Number of patients	%	Number of patients	%
0	393	47.1	404	48.4
1	205	24.6	241	28.9
2	133	15.9	137	16.4
3	58	6.9	41	4.9
4	33	4.0	10	1.2
5	12	1.4	2	0.2
6	1	0.1	0	0.0
Total	835	100.0	835	100.0

emergency medicine services. In 2002, 58.0% of the population aged ≥75 years presented to emergency departments at least once in the United States. This rate corresponds to 39.0% of the total population (7).

This information suggests that the workload in emergency departments everywhere is expected to increase with the increase in the older population. The present study yields important data about polypharmacy and inappropriate drug use in elderly patients admitted to the emergency department.

In terms of comorbidities, Ünsal et al. reported in 2003 that patients aged ≥65 years presented most commonly to the emergency department because of hypertension (HT) and cardiovascular diseases (8). In the present study, the comorbidities were, in descending order of frequency, HT (69.5%), coronary artery disease (CAD) (41.8%), diabetes mellitus (DM) (26.9%), chronic obstructive pulmonary disease (COPD) (21.2%), and congestive heart failure (CHF) (12.3%). In this study, diseases such as HT, CAD, DM, COPD, and CHF were more frequently encountered probably because the data were collected from the emergency department.

The increase in the number of chronic diseases is considered to be one of the most important risk factors for polypharmacy. In the present study, we found that 44.2% of the patients were using six or more drugs and 18.0% of the patients were using 10 or more drugs. In this study, the average number of drugs was 6.6 ± 3.2. Kaufman et al. conducted a study in the United States in 2002, wherein they reported polypharmacy in 57.0% of females and 44.0% of males aged ≥65 years. In the same study, they found that 12.0% of females and males were using 10 or more drugs (9).

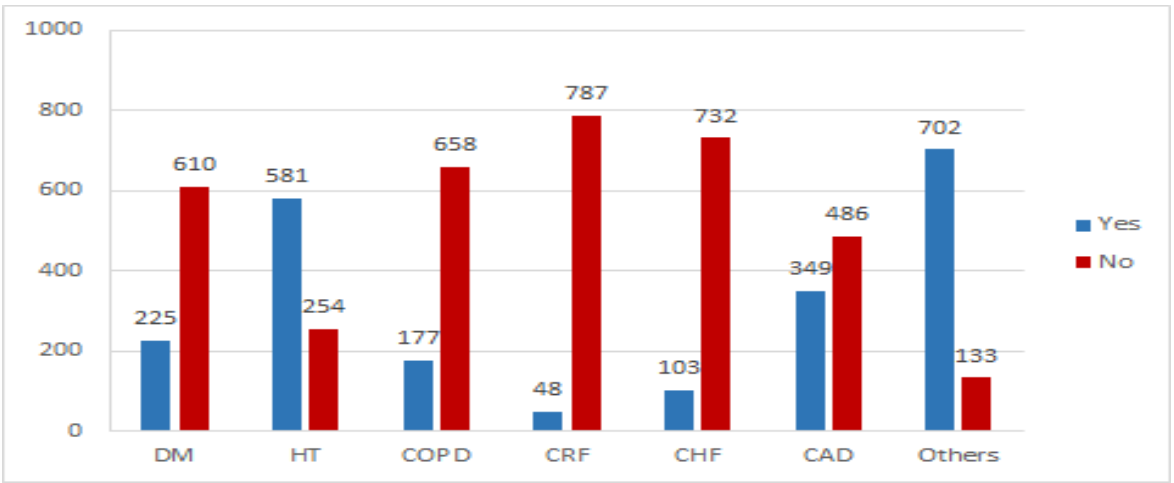
In this study, the prevalence of inappropriate drug use was 51.6% according to the STOPP Version 2 Criteria and 52.9% according to the 2012 Beers Criteria. The worldwide prevalence of inappropriate drug use was reported to be 13.0%–35.0% according to the STOPP Version 2 and 2012 Beers Criteria (10). In a 2012 study by Blanco-Reina et al., the prevalence of inappropriate drug use was 24.3% according to 2003 Beers, 35.4% according to STOPP Version 1, and 44.0% according to 2012 Beers Criteria in 407 elderly patients admitted to primary healthcare centers (11). In a 2014 study by Jhaveri et al., the rate of inappropriate drug use was quite high according to the 2012 Beers Criteria (87.3%) in 676 elderly patients (average age, 72.7 years) who were hospitalized in tertiary healthcare centers (12). Davidoff et al. investigated the prevalence of inappropriate drug use in the United States in 2015 in 18 475 elderly patients and reported that the rate was 40.8% between 2006 and 2010 according to the 2012 Beers Criteria. In the United States, the most common inappropriately used drug was NSAID (10.9%) according to the 2012 Beers Criteria (13).

In a study by Lam et al. in 2015 with elderly patients treated and hospitalized in a tertiary healthcare center, it was reported that the rate of inappropriate drug use was 31.6% and 38.6% according to the STOPP Version 1 and 2012 Beers Criteria, respectively (14).

This study showed that NSAIDs are one of the most common inappropriately used drug classes. The use of NSAIDs is associated with increased gastrointestinal and cardiovascular risks, particularly in older patients. NSAIDS are also more likely to cause problems in renal function in older patients. Furthermore, a recent study found that NSAIDs constitute an independent risk factor for community-acquired hyperkalemia (15).

It is known that the inappropriate use of NSAIDs may cause gastric irritation, chronic blood loss, anemia, sodium retention, and kidney failure, particularly in patients aged >65 years. Drug-induced nephrotoxicity is likely to reduce the effectiveness of antihypertensive drugs. The use of NSAIDs is associated with a two-fold increased risk of chronic kidney disease, especially in patients aged >65 years. Furthermore, inappropriate use of NSAIDs is reported in patients with kidney failure (16, 17, 18).

Figure 1. Comorbidities of the patients.



DM, diabetes Mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CHF, congestive heart failure; CAD, coronary artery disease.

In the present study, 35 patients presented to the emergency department after a fall. According to the STOPP Version 2 Criteria, 20.0% of these patients were taking drugs with apparent anticholinergic activity. It is known that inappropriate drug use increases the risk of falls in older patients. This is mostly associated with anticholinergic medications, as well as long-term use of benzodiazepines and psychotropic medications. Primary healthcare providers must pay special attention when prescribing medications with anticholinergic effects (e.g., tricyclic antidepressants and antihistamines) to elderly patients (19, 20).

An emphasis on inappropriate drug use will help physicians in the emergency department and other healthcare professionals reduce side effects and complications of medications and potentially reduce emergency admissions to hospitals. Thus, healthcare providers should pay more attention to inappropriate drug use, drug–drug interactions, and possible side effects of drugs, particularly in patients aged >65 years. It should also be emphasized that the 2012 Beers and STOPP Version 2 Criteria are developed not to replace physicians' decisions but to guide them to appropriately prescribe medications.

This study has some limitations. This study was conducted in the emergency department. Therefore, no detailed information about patients, such as glomerular filtration rate or systolic ejection fraction, was available. Because there was no information regarding where patients lived, no comparison was made between patients living in their home and those living in geriatric care centers. This study was conducted in only one healthcare center.

In conclusion, inappropriate drug use is a major healthcare problem across the world. The 2012 Beers and STOPP Version 2 Criteria used in this study are not intended to replace clinical assessment but rather to facilitate and support clinical processes. Therefore, these criteria cannot be the only sources of information that guide medication choice. The aim of these criteria is to protect patients from the side effects of drugs and improve the quality of treatment while prescribing a minimum number of drugs. Based on the

findings of the present study, the 2012 Beers and STOPP Version 2 Criteria are recommended as a resource for prescribing drugs for elderly patients with the added benefit of improving the quality of healthcare services. The present study and previous worldwide studies suggest that these criteria are effective methods for determining inappropriate drug use.

To the best of our knowledge, the present study is the first investigation on the use of the STOPP Version 2 and 2012 Beers Criteria to analyze polypharmacy and inappropriate drug use among elderly patients admitted to an emergency department and is considered to play a guiding role to healthcare services for the elderly in Turkey and around the world.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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RESEARCH

AN ASSESSMENT OF MOBILITY AND FALL BEHAVIOUR AMONG OLDER PATIENTS ADMITTED TO THE ORTHOPAEDIC OUTPATIENT CLINIC

Abstract

Introduction: Unintentional falls in older individuals can lead to fatal and non-fatal injuries. This study aimed to determine the risk factors for falls among elderly patients and to specify the timely safety measures that can be taken to prevent falls in the elderly population.

Materials and Method: This study is a descriptive, cross-sectional study of containing 178 older patients. Data for the study were collected with the sociodemographic questionnaire form, Rivermead Mobility Index and the Falls Behavioural Scale for the Older Persons.

Results: The mean age of the 178 patients in this study was 67.14±5.95 years and 56.7% (n=101) were female, 43.3% (n=77) were male. The patients who had a fear of falling and the patients who fell within the previous year; had a statistically significant level of low physical activity (p=0.019, p=0.033). Males (p=0.002), those aged 80 years and above, married patients, high school graduates, those on continuous medication and those who fell within the previous year had higher mean Falls Behavioural Scale scores (p<0.001).

Conclusion: It may be beneficial to make the necessary arrangements that would not pose a risk in neighbourhoods populated by older adults; to assess their level of mobility when they show up for routine examination; to take adequate safety measures after determining their needs according to their mobility status and to organize the prescribed drugs according to falling probability.

Keywords: Aged; Orthopaedics; Accidental falls; Geriatrics; Movement

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ARAŞTIRMA

ORTOPEDİ POLİKLİNİĞİNE BAŞVURAN YAŞLI HASTALARIN MOBİLİTE VE DÜŞME DAVRANIŞLARININ DEĞERLENDİRİLMESİ

Öz

Giriş: Yaşlı bireylerde istenmeyen düşmeler sonucu; ölümcül olan ve olmayan yaralanmalar meydana gelebilir. Bu çalışma yaşlı hastalarda düşme ile ilgili risk faktörlerini saptamak ve özellikle yaşlılarda düşmenin önlenmesi için zamanında alınabilecek güvenlik önlemlerini belirlemek için yapılmıştır.

Gereç ve Yöntem: : Tanımlayıcı, kesitsel bir çalışma olan araştırmamıza 178 yaşlı hasta dahil edilmiştir. Çalışma verileri; sosyodemografik anket formu, Rivermead Mobilite İndeksi ve Yaşlılar İçin Düşme Davranışları Ölçeği kullanılarak toplanmıştır.

Bulgular: Çalışmamıza katılan 178 hastanın yaş ortalaması 67.14±5.95 olup; %56.7'si kadın (n=101), %43.3'ü erkekti (n=77). Düşme korkusu olan hastaların ve son 1 yıl içinde düşme öyküsü olan hastaların anlamlı derecede fiziksel aktivite yapmadığı belirlendi (p=0.019, p=0.033). Yaşlı erkeklerin (p=0.002), 80 yaş ve üzerinde olanların, evlilerin, lise mezunu olanların, sürekli ilaç kullanımı olanların, son bir yıl içinde düşenlerin; Yaşlılar İçin Düşme Davranışları Ölçeği'ne göre puan ortalamaları anlamlı derecede daha yüksektir (p<0.001).

Sonuç: Yaşlı bireylerin yaşadıkları çevrede risk oluşturmayacak şekilde gerekli düzenlemelerin yapılması, periyodik muayeneye geldiklerinde mobilite düzeylerinin tespit edilmesi, ihtiyaçlarının mobilite durumuna göre belirlenerek yeterli güvenlik önlemlerinin alınması ve yaşlılara yazılan reçetelerin düşme ihtimalleri göz önüne alınarak yeniden düzenlenmesi erken dönemde düşmelerin önlenmesinde faydalı olabilir.

Anahtar sözcükler: Yaşlı; Ortopedi; Düşmeler; Geriatri; Mobilite

INTRODUCTION

In both Turkey and the rest of the world, the elderly population is growing and life expectancy is increasing with each passing day. The population aged 65 years or above has grown significantly relative to the total population in Turkey over the years. While the elderly population was 3.5% of the total population in 1940, it rose to 4.4% in 1970, 7.5% in 2012 and 8.3% in 2016. Elderly population, which is defined as the population aged 65 years and above, is projected to increase to 10.2% in 2023, 16.3% in 2040, 22.6% in 2060 and 25.6% in 2080 (1).

Senescence is an inevitable phase that generally involves reduced perception and awareness, gradually deteriorating memory functions as well as physiological and mental changes that all humans will experience. According to the data of the Centre for Disease Control and Prevention (CDC), more than one-third of the adult population is at the age of 65 years and above (2). The data from the World Health Organization shows that 28%–35% of the older individuals aged 65 years and above experience falls, and that the prevalence of falls increases each year with age (3, 4). These unintentional falls in older individuals can lead to non-fatal and fatal injuries. Nearly 20%–30% of falls are classified as moderate-to-severe injuries that require medical care and hospitalization (5). These injuries can have consequences including increased need for home healthcare services, loss of independence and increased rate of premature death in older adults (6). Risk factors include reduced muscle strength, visual impairment, diabetes, urinary incontinence, arthritis, dizziness, Alzheimer's disease, depression, orthostatic hypotension, cognitive impairment, polypharmacy, persistent pain and some of the prescribed drugs (2). Studies have shown that psychological stress also has a significant effect on falls among the elderly (7, 8). It was found that, following recurrent falls, older adults tended to develop such a fear of falling that it led to loss of physical activity, which in turn led to a higher risk of falling (9). Studies have also shown that nurses, physicians and therapists could help reduce the rate of falls by 20%–30% when they work together and help the patients take the necessary precautions (10).

In 2010, approximately 2.3 million older adults with non-fatal fall-related injuries were treated in emergency departments. The direct medical cost of falls was 30 billion USD in 2010, and it is projected that annual direct and indirect costs of fall-related injuries will rise to 67.7 billion USD by 2020 (11). In another study, it was found that falls made a significant contribution to the costs, and that this was especially valid for hospitalisation periods of more than 8 days (12). Considering the economic burden associated with falls, it would be highly beneficial to take the necessary precautions and make interventions to minimise the risk of falling.

This study aimed to determine the risk factors for falls among elderly patients and to specify the timely safety measures that can be taken to prevent falls in the elderly population.

MATERIALS AND METHOD

This study is a descriptive, cross-sectional study. The study group consisted of 178 older patients who were admitted to the Orthopaedics and Traumatology Outpatient Clinic between 1 November 2018 and 1 December 2018. All elderly patients who were admitted to the orthopaedic outpatient clinic between the specified dates, who volunteered to participate in the study, who were able to communicate and who were not diagnosed with dementia were included in this study. All the elderly patients volunteered to participate in the study with provided informed consent. Data for the study were collected with the sociodemographic questionnaire form, Rivermead Mobility Index (RMI) and the Falls Behavioural Scale (FaB) for the Older Persons. The approval for this study was obtained from the Non-Interventional Clinical

Research Ethics Committee of Selcuk University Faculty of Medicine with its decision number 20, dated 24.10.2018.

Socio-demographic Questionnaire Form: The questionnaire included socio-demographic characteristics of the patients (gender, age, body mass index, marital status, education status, regular physical activity status) and information about use of continous medication.

Rivermead Mobility Index (RMI): RMI was developed by Collen et al. (13), and the validity and reliability study of the index's Turkish version was performed by Akın and Emiroğlu (14). RMI is a unidimensional index that includes the basic mobility activities, and it was prepared to assess the mobility status of older patients (13). This index comprises 14 questions, 13 of which are patient self-reported items to measure mobility. Only Item 5 is filled out by the interviewer based on direct observations. Each question in the index receives a score of either 0 or 1. After scoring, the lowest possible score on this index is '0', while the highest possible score is '15'. A total score of 15 indicates that there are no mobility problems, whereas total scores of 14 and lower indicate that there is a mobility problem (14).

Falls Behavioural Scale for the Older Person (FaB): The scale was developed in 2003 by Clemson, Cuming and Heard (15), and the validity and reliability study for the Turkish version of the index was performed by Uymaz and Nahcivan in 2013 (16). This scale was developed to reveal the awareness and behaviours of older adults in terms of protecting themselves from potential falls in their daily lives. The scale consists of 30 items and has 10 sub-dimensions. These sub-dimensions consist of cognitive adaptation, protective mobility, avoidance, awareness, pace, practical strategies, changes in the activity plan, being observant, changes in level and getting to the phone. Each sub-dimension is scored from 1 to 4. The lowest score from the scale is '1', while the highest score is '4', such that the score ranges between 1 and 4. Except for Items 7, 8, 9, 10, 19 and 23 on the scale, responses to the other items are scored as follows: 'never' 1 point, 'sometimes' 2 points, 'often' 3 points and 'always' 4 points. The score for each sub-dimension is individually calculated by dividing the total score of all sub-dimensions by the number of items. High scores show the preventive and safe behaviours of patients in relation to falls, whereas low scores show risky patient behaviour in relation to the same (5).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science version 22.0 software. In data analysis, descriptive statistics were provided with frequency (n), percentage (%), mean ± standard deviation, and min–max values. Regarding statistical significance, non-parametric Mann–Whitney U test was used to compare the data according to continuous variables, Kruskal–Wallis H test was used to compare more than two groups and Bonferroni Test was used to determine between which groups there was a difference. Normal distribution of the data was analysed using the Kolmogorov–Smirnov test of normality. A p value<0.05 was accepted as statistically significant.

RESULTS

Of the patients, 56.7% (n=101) were female and 43.3% (n=77) were male. The mean age of the 178 patients who were enrolled in our study was 67.14±5.95 years (min: 60, max: 83). Furthermore, 69.1% (n=123) of the patients were married, while 30.9% (n=55) of the patients were either single or widowed. Among the patients, 48.3% (n=86) were primary school graduates and 24.7% (n=44) were high school graduates. It was observed that 64.6% (n=115) of the patients were on continuous medication, whereas 35.4% (n=63) were not. The mean body mass index (BMI) of the patients was 31.18±4.58 (min: 23.00, max: 46.10) kg/m2. Regular physical activity; regular, planned and repeated

physical activities aimed at the protection or development of one or more components of physical fitness. Also, 69.61% (n=123) of the patients did not regularly engage in physical activity (Table 1).

Of the patients, 58.4% stated that they experienced a fear of falling, whereas 41.6% said that they never felt such a fear. In addition, 51.1% of the participants said that they fell at least once, whereas 48.9% said that they did not fall within the recent year. A total of 91 patients said that they fell at least once; 32.6% of those who fell within the recent year stated that they fell three times or more, whereas 15.2% and 3.4% stated that they fell twice and once, respectively (Table 2).

The mean RMI score of the older patients was 9.31±1.72. The mean FaB score of the patients was 2.71±0.21. Analysing the sub-dimensions of the scale, the highest mean score belonged to 'being observant' with 2.94±0.86 and 'awareness' with 2.94±0.27, whereas the lowest mean score belonged to 'change in the activity plan' with 1.78±0.55 (Table 3).

The mean RMI scores of the elderly patients who were admitted to the orthopaedic outpatient clinic exhibited a statistically significant difference according to gender, with females having a higher mean score in comparison to males (p=0.009). The mean RMI scores of the patients also exhibited a statistically significant difference according to age (p<0.001), with such a difference being observed between the 60–65-year age group and the 66–79-year age group (p<0.001), and also between the 60–65-year age group and the group aged 80 years and above (p<0.001). A statistically significant difference was noted between the mean RMI scores according to marital status, and single and widowed patients had a higher mean score in comparison to the married patients (p<0.001). The mean RMI scores exhibited a statistically significant difference according to education status, and such difference was observed between literate patients and high school graduates (p=0.03), and between primary school graduates and high school graduates (p<0.001). A statistically significant difference was noted between the mean RMI scores according to the continuous use of medication, with patients who were not on continuous medication having a higher mean score than those on continuous medication (p<0.001). The mean RMI scores exhibited a statistically significant difference according to the fear of falling, wherein patients who did not experience a fear of falling had a higher mean score than those who experienced this fear (p<0.001). The mean RMI scores exhibited a statistically significant difference according to the incidence of falls within the last year, with patients who did not fall within the previous year having a higher mean score than those who did (p=0.019) (Table 4).

A statistically significant difference was noted between mean RMI scores according to the BMI groups, with such a difference being observed between the group with a BMI of 18.5–24.9 kg/m2 and the group with a BMI of 25.0–29.9 kg/m2, and also between the group with a BMI of 18.5–24.9 kg/m2 and the group with BMI≥30kg/m2 (p=0.005). Considering the mean FaB score of the older patients, it was found that males (p=0.002), those aged 80 years and above, married patients, high school graduates, those on continuous medication and those who fell within the previous year had higher mean FaB scores, and the difference between the groups was also statistically significant (p<0.001) (Table 4).

DISCUSSION

This study aimed to evaluate the mobility and fall behaviour of elderly patients who were admitted to the orthopaedic outpatient clinic and found that 51.2% of the older patients fell within the previous year, and that 32.6% of these patients had fallen three times or more. According to the WHO data, the prevalence of falls among older adults is

Table 1. Sociodemographic characteristics of the patients.

Variable	Category	n	%
Gender	Female	101	56.7
	Male	77	43.3
Age, Mean±SD (min-max) **67.14±5.95 (60-83)**			
Age groups	Between 60-65	102	57.3
	Between 66-79	64	36.0
	80 and above	12	6.7
Marital status	Married	123	69.1
	Single+Widowed	55	30.9
Education status	Literate	26	14.6
	Primary School	86	48.3
	High School	44	24.7
	University and higher	22	12.4
Continuous medication	Yes	115	64.6
	No	63	35.4
BMI, mean±SD (min-max) **31.18±4.58 (23.00-46.10)**			
BMI groups	18.5-24.9	7	3.9
	25.0-29.9	65	36.5
	≥30	106	59.6
Regular physical	Yes	55	30.9
Activity status	No	123	69.1
Total		**178**	**100.0**

Mean±SD: Mean ± standard deviation, BMI: Body mass index

28%–35% for those living in their home, and even higher (i.e. 30%–50%) for those living in a nursing home (3, 17). The prevalence we found in our study was higher than that reported in China (18%) (18), Sweden (19.1%) (19) and Nigeria (23%) (20), and lower than that reported in Egypt (60.3%) (21). This difference may stem from many behavioural, environmental, psychological and biological factors. Another problem that affects elderly adults is the fear of falling. In our study, 58.4% of the older adults stated that they experience a fear of falling. Other studies reported that 66% of older women in Netherlands (22), 84% of older women in Korea (23) and 35% of older women in the United

Table 2. Distribution of older patients according to their characteristics concerning the history of falls (n=178).

Variable	Category	n	%
Experienced fear of falling	Yes	104	58.4
	No	74	41.6
Fell within the recent year	Yes	91	51.1
	No	87	48.9
Number of falls[a] (n=91)	Once	6	3.4
	Twice	27	15.2
	3 times or more	58	32.6

[a]Includes the patients who reported that they fell at least once within the recent year.

States (24) experience a fear of falling. The varying prevalence of fear of falling in each society could be due to the differences in cultural structure, history of falls, age distribution and so on.

The falls and the fear of falling experienced by older adults are essentially due to their mobility problems. We observed the mobility status of patients using RMI. Considering the fact that older patients who receive a score of 14 or less have mobility problems, we found that there were mobility problems as the mean RMI score of the patients who participated in our study was 9.31±1.72. According to another study, the mean RMI score of 124 older adults living in a nursing home was 10.27±4.25, indicating that they had mobility problems (25). Scimia et al. measured the RMI scores of 108 patients aged 80 years and above upon admission (RMI1) and after a daily 6-minute walk test (RMI2), and found a mean RMI1 score of 8.5±3.4 and a mean RMI2 score of 13.1±2.9, thus observing that the RMI score was positively affected by cardiac rehabilitation (26). This indicates that mobility-related problems increase with advancing age.

There was a statistically significant relationship between the mean RMI scores and gender, age, marital status, education status, continuous use of medication, the fear of falling, a history of fall within the previous year and BMI (Table 4). Wu et al. reported in their study conducted on 671 elderly adults that female gender, age-related bone weakness and polypharmacy were associated with increased risk of falling (27). In a study by Okuyan and Bilgili, a statistically significant relationship was observed between gender, education status, age, the fear of falling, physical activity status and mean RMI scores (25). Although the prevalence of mobility problems is reportedly higher in females according to the literature, we found that the prevalence of mobility problems was significantly higher in males. In our study, we also found a significant correlation between the continuous use of medication, advanced age and mean RMI scores, which is consistent with the literature.

We did not find a significant relationship between physical activity status and RMI, while older patients who had a fear of falling and fell within the previous year did not have a statistically significant level of physical activity. Lim et al. conducted a study on 438 females aged 65 years and above, and reported that physical inactivity was an important risk factor that could be accountable for recurrent falls (28). According to the literature,

Table 3. Mean RMI and FaB Scores.

Scales and sub-dimensions	Cronbach's alfa	Mean±SD	Min-Max
RMI	.81	9.31±1.72	2-15
FaB Sub-dimensions			
Cognitive adaptation	.70	2.85±0.26	2.5-3.1
Protective mobility	.63	2.60±0.61	1.8-3.2
Avoidance	.56	2.76±0.27	2-3
Awareness	.53	2.94±0.27	2.2-3.2
Pace	.60	2.85±0.46	2-3.5
Practical strategies	.52	2.56±0.28	2-3
Changes in the activity plan	-	1.78±0.55	1-3
Being observant	-	2.94±0.86	1-4
Changes in level	.61	2.31±0.24	2-2.5
Getting to the phone	-	2.79±0.40	2-3
FaB total	.85	2.71±0.21	2.4-3

RMI: Rivermead Mobility Index; FaB: Falls Behavioural Scale for the Older Person; Mean±SD: Mean±standard deviation.

a physically inactive life is considered to be a risk factor for falls (25, 28). On the basis of all these results, we may say that older patients who have a history of falling also have a lower level of physical activity due to their fear of falling.

In our study, the mean FaB score, which is a measure of protective mobility practised by older adults to protect themselves from potential falls throughout the day, was 2.71±0.21. Considering that the lowest score is 1 and that the highest score is 4 on this scale, it can be stated that elderly patients engage in a moderate level of protective behaviour to protect themselves from falls. Okuyan and Bilgili found a mean FaB score of 2.99±0.56 (25). These results imply that elderly adults do not have sufficient falls awareness. The mean scores of all sub-parameters of the scale were lower than 3 in our study (Table 3). Okuyan and Bilgili found the mean scores to be higher than 3 in the sub-dimensions of cognitive adaptation, avoidance, awareness, pace, changes in the activity plan and changes in level, and observed the older adults had a better protection from falls (25).

The fact that the elderly population is growing at a fast pace puts great responsibilities on physicians, especially on primary care physicians, with regard to falls among the elderly. Our study showed that the frequency of falls was high in elderly adults who are admitted to the orthopaedic outpatient clinic. In daily orthopaedic practice; clinicians always focus to stop pain and prescribes narcotics, pregabalin, gabapentine or tizanidine so often for geriatric population with the diagnoses "spinal stenosis, gonarthrosis, coxarthrosis and the other degenerative and rheumotologic problems ". These prescribes turn a continous usage at the family medicine clinics for geriatric population. The adverse affects of these drugs as causes of

Table 4. Comparison of mean RMI and FaB scores according to several patient characteristics.

			RMI			FaB		
Variable	**Category**	**n**	**Mean±SD**	**x2**	**P**	**Mean±SD**	**x2**	**P**
					f/z			**f/z**
Gender[b]	Female	101	9.57±1.82	2.612	0.009*	2.62±0.20	3.071	0.002*
	Male	77	9.15±1.47			2.79±0.20		
Age groups[a]	Between 60-65	102	9.83±1.99	33.172	<0.001*	2.59±0.15	52.679	<0.001*
	Between 66-79	64	8.77±0.79			2.82±0.22		
	80+	12	8.60±0.54			2.95±0.03		
Marital status[b]	Married	123	9.28±1.87	5.220	<0.001*	2.79±0.19	8.730	<0.001*
	Single+Widowed	55	9.60±1.22			2.49±0.03		
Education status[a]	Literate	26	9.00±0.01	48.369	<0.001*	3.00±0.01	82.400	<0.001*
	Primary School	86	9.18±1.39			2.66±0.18		
	High School	44	9.81±2.46			2.70±0.23		
	University and higher	22	9.61±1.38			2.50±0.01		
Continuous use of medication[b]	Yes	115	9.06±1.35	6.660	<0.001*	2.81±0.19	8.757	<0.001*
	No	63	9.92±2.03			2.50±0.04		
Experienced fear of falling[b]	Yes	104	9.10±0.90	3.587	<0.001*	2.71±0.23	0.709	0.479
	No	74	9.80±2.35			2.67±0.19		
Fell within the previous year	Yes	91	9.20±1.43	2.351	0.019*	2.79±0.21	4.403	<0.001*
	No	87	9.62±1.94			2.57±0.14		
BMI groups[a]	18.5-24.9	7	12.50±2.34	10.444	0.005*	2.51±0.06	3.597	0.166
	25.0-29.9	65	9.74±1.54			2.72±0.21		
	≥30	106	8.92±1.31			2.70±0.22		

*= represents significance at p<0.05 level; a: Kruskal–Wallis H test was performed; b: Mann–Whitney U test was performed.

suddenly falls are known in the literature with the high evidence studies and we try to highlighten this point in the conclusion part. Clinicians may prefer to solve the main reasons of pain, instead of just killing the pain only. The majority of older adults experienced a fear of falling and refrained from physical activity. According to our study, factors such as the male gender, advanced age, being married, high BMI, continuous use of medication, a fear of falling and having a history of falls in the previous year negatively affected the mobility level, and constituted a risk for falling. Physicians who treat and perform follow-ups for elderly patients should primarily provide trainings on safe/protective and risky behaviours for their patients in order to prevent falls. Older adults should also be

encouraged to engage in regular physical activity. In the short-term, it may be beneficial to make the necessary arrangements that would not pose a risk in neighbourhoods populated by older adults; to assess their level of mobility when they show up for routine examination; to take adequate safety measures after determining their needs according to their mobility status and to reduce the number of unnecessary drugs prescribed to older adults.

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RESEARCH

THE EFFECT OF SPINAL ANESTHETIC TECHNIQUE ON NEUTROPHIL TO LYMPHOCYTE RATIO AND POSTOPERATIVE MORTALITY IN ELDERLY PATIENTS WITH CORONARY ARTERY DISEASE UNDERGOING HIP REPLACEMENT SURGERY

Abstract

Introduction: This study aimed to determine the effect of anesthetic techniques on the neutrophil-to-lymphocyte ratio in elderly patients with coronary artery disease who underwent hip replacement surgery.

Materials and Method: In this retrospective cohort study, we reviewed the medical records of 41 elderly patients with coronary artery disease who underwent hip replacement surgery between January 2015 and September 2017. The following data were collected: demographic characteristics; neutrophil-to-lymphocyte ratio measured preoperatively (T0; baseline), on postoperative day 1 (T1), and on postoperative day 2 (T2); anesthetic technique; surgery duration; postoperative complications; and postoperative 1-year mortality.

Results: In total, 41 patients were included, of which 14 (34.1%) were men and 27 (65.9%) were women; the mean age was 77.8±7.89 (range, 65–95) years. The baseline neutrophil-to-lymphocyte ratio (T0) was 6.22±3.8 increased to 10.66±11.47 on T1 and 8.75±7.81 on T2. neutrophil-to-lymphocyte ratio on T2 was significantly higher in patients receiving general anesthesia than in those receiving spinal anesthesia (p=0.032). Within 1 year after surgery, seven (30.6%) deaths were reported: one patient who received spinal-epidural anesthesia and 6 patients who received general anesthesia (p=0.044). The area under the curve for neutrophil-to-lymphocyte ratio on T2 was 0.79 (95% CI, 0.625–0.955; p=0.017) with an optimal cutoff value of 5.18.

Conclusion: Neutrophil-to-lymphocyte ratio on T2 is a risk factor for 1-year mortality in elderly patients with coronary artery disease who underwent hip replacement surgery. Spinal anesthesia was observed to be associated with a lower mortality rate by minimizing neutrophil-to-lymphocyte ratio value on T2 than general anesthesia.

Keywords: Hip fractures; Geriatrics; Neutrophils; Lymphocytes; Anesthesia; Coronary artery disease

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ARAŞTIRMA

KALÇA PROTEZİ AMELİYATI GEÇİREN KORONER ARTER HASTALIĞINA SAHİP YAŞLI HASTALARDA SPİNAL ANESTEZİK TEKNİĞİN NÖTROFİL LENFOSİT ORANI VE POSTOPERATİF MORTALİTE ÜZERİNE ETKİSİ

Öz

Giriş: Bu çalışmada, kalça protezi ameliyatı geçiren koroner arter hastalığına sahip yaşlı hastalarda anestezi tekniklerinin nötrofil-lenfosit oranı ve postoperatif mortalite üzerine etkisini belirlemek amaçlanmıştır.

Gereç ve Yöntem: Retrospektif kohort çalışmamızda, Ocak 2015-Eylül 2017 tarihleri arasında kalça protezi ameliyatı geçirmiş koroner arter hastası olan geriatrik hastaların tıbbi kayıtlarını inceledik. Hastaların demografik özellikleri, uygulanan anestezik teknikleri; ameliyat süresi; ameliyat sonrası komplikasyonlar; ve postoperatif 1 yıllık mortalite ile ameliyat öncesi (T0; taban çizgisi), ameliyat sonrası 1. günde (T1) ve ameliyat sonrası 2. günde (T2) nötrofil-lenfosit oranı ölçüldü.

Bulgular: 14'ü (% 34,1) erkek, 27'si (% 65,9) kadın; yaş ortalaması 77.8 ± 7.89 (dağılım, 65–95) olan toplamda 41'i hasta çalışmaya dahil edildi. Bazal nötrofil-lenfosit oranı (T0) 6.22 ± 3.8 idi, T1'de 10.66 ± 11.47'ye ve T2'de 8.75 ± 7.81'e yükseldi. Genel anestezi alan hastalarda T2'deki nötrofil-lenfosit oranı , spinal anestezi alanlara göre anlamlı derecede yüksekti (p = 0.032). Ameliyattan sonraki 1 yıllık mortaliteye bakıldığında, spinal-epidural anestezi alan bir hasta ve genel anestezi alan 6 hasta (p = 0.044) olmak üzere yedi (% 30.6) ölüm rapor edildi. T2'deki nötrofil-lenfosit oranı eğrisi altındaki alan 0.79 , optimum cut-off değeri ise 5.18 (% 95 CI, 0.625-0.955; p = 0.017) idi.

Sonuç: T2'deki nötrofil-lenfosit oranı, kalça protezi ameliyatı geçiren koroner arter hastalığı olan yaşlı hastalarda 1 yıllık mortalite için risk faktörüdür. Spinal anestezinin, genel anesteziden ziyade T2'deki nötrofil / lenfosit oranını en aza indirerek düşük mortalite oranı ile ilişkili olduğu gözlendi.

Anahtar sözcükler: Kalça kırığı; Geriatri; Nötrofil; Lenfosit; Anestezi; Koroner arter hastalığı

INTRODUCTION

With improvements in living standards, the prolongation of human life has resulted in a rapidly growing aging population. Emergent conditions such as systemic diseases, reduction in reflexes, and cerebrovascular events may cause greater exposure to environmental trauma in the elderly population. In addition, the reduced bone mass in the elderly increases the incidence of fracture (1); the most commonly occurring extremity fractures are now viewed as a geriatric epidemic. The incidence of hip fractures (HF), which are usually associated with low-energy trauma, has increased with the growing aging population. Surgery is the best treatment option for elderly patients to regain functional abilities. Because HF occurs predominantly in elderly patients, a high prevalence of underlying coronary artery disease (CAD) can be expected (2). The adaptive capacity of elderly patients is low; moreover, concomitant diseases, particularly cardiovascular diseases (CVD), are often present. Therefore, hip replacement surgery may cause increased morbidity and mortality in elderly patients. The incidence of perioperative myocardial ischemia in elderly patients undergoing HF surgery has been reported to be 35%-2% (3). In recent systematic reviews, mortality within 1 year following HF surgery has been shown to increase from 8.4% to 36% (4,5).

Hip replacement surgery is widely performed in the elderly patients; however, there are controversies regarding the ideal anesthetic technique, particularly in elderly patients with CVD (6). The use of local anesthesia may be the key anesthetic technique to decrease the risk of postoperative complications in patients undergoing hip replacement surgery. The most notable outcomes associated with neuraxial anesthesia include avoidance of intubation and mechanical ventilation and a decrease in blood loss and postoperative analgesia use. However, general anesthesia may offer better hemodynamic stability than neuraxial anesthesia (7).

The neutrophil-to-lymphocyte ratio (NLR) is a popular hematological parameter used as an indicator for subclinical inflammation. NLR is an inexpensive and widely used independent biomarker of morbidity and mortality caused by CVD, particularly CAD. In addition, NLR has been shown to be a risk factor for postoperative mortality and cardiovascular complications in patients undergoing HF repair (8).

This study aimed to investigate the effects of anesthetic techniques on NLR and determine their impact on postoperative mortality in elderly patients with CAD who underwent hip replacement surgery.

MATERIALS AND METHOD

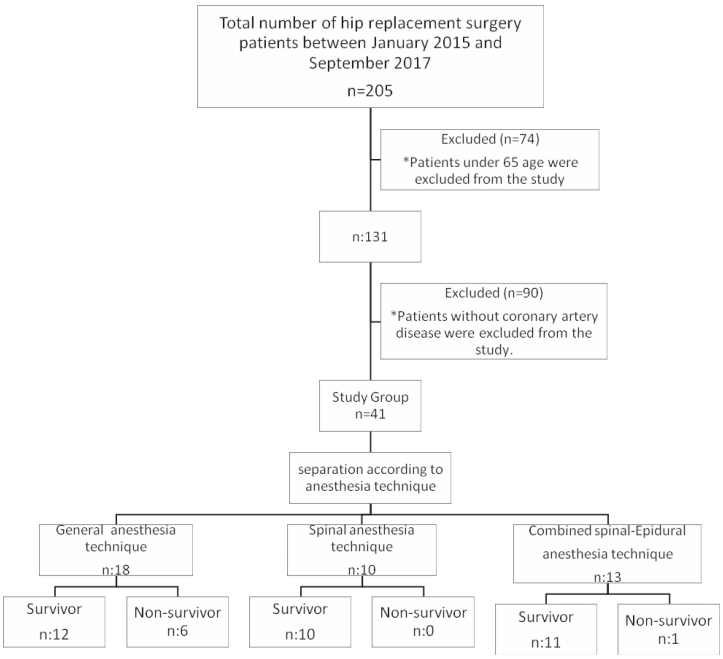
Study plan

In this retrospective cohort study, we reviewed the medical records of 41 elderly patients with CAD who underwent hip replacement surgery between January 2015 and September 2017. The following data were evaluated for each patient: demographic characteristics, laboratory parameters, anesthetic techniques, surgery duration, postoperative complications, and 1-year mortality. The follow-up period was completed in October 2018. Approval for the study was granted by University Medical Faculty Ethics Committee (Approval No. 11; date, February 1, 2018).

Aims of the study and Patient selection

Primarily, we aimed to investigate the effect of anesthetic techniques on NLR in elderly patients with HF and a history of CAD who underwent hip replacement surgery. Our secondary aim was to determine the effect of these techniques on postoperative 1-year mortality and to evaluate the survival period, which was measured from the date of the hip surgery to the last follow-up. The patients included in the study were aged ≥65 years, underwent hip replacement surgery and had a history of CAD (Figure 1).

Figure 1. Consort diagram



Laboratory assessment

Blood samples were obtained from each patient in our bioclinical laboratories preoperatively (T0; baseline) and on postoperative days 1 (T1) and 2 (T2). The blood samples were processed in a blood analyzer (CELL-DYN Ruby hematology analyzer, Abbott, USA) to detect differential whole blood cell and leukocyte counts based on ethylenediaminetetraacetic acid anticoagulants. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Survival status

The survival status of each patient (alive or dead) and the date of death (if any) were retrieved from the Turkish Central Civil Registration System (MERNIS) using the national ID numbers of the patients. However, the cause of death was unavailable in the system.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp). Continuous variables were expressed as mean±standard deviation (SD); categorical variables were expressed as frequencies and percentages. The normal distribution of data was determined using histograms, the Kolmogorov–Smirnov test and Shapiro-wilk test. As the NLR value showed nonnormal distribution, Friedman test was performed to compare time-dependent changes in these parameters. The groups were compared using Kruskal-Wallis H test. Kruskal-Wallis H test was applied to non-parametric data with a 95% confidence interval and p level of <0.05 was accepted significant. In the presence of a significant difference between the data sets, two groups were compared using Mann-Whitney U test to determine whether the differences between the groups were significant.

Relationship between the choice of anesthetic technique and mortality was analyzed using Chi-square test.

Correlations between continuous variables were determined using Spearman's Correlation Coefficient. The receiver-operating characteristic (ROC) curve analysis was performed to identify the sensitivity and specificity of NLR to predict 1-year mortality. A two-tailed test was applied, and a p value of <0.05 was considered to be significant.

RESULTS

Patient characteristics

In total, 41 ASA III patients with CAD who underwent cemented total hip replacement because of unstable trochanteric fracture were included in the study; of these, 14 (34.1%) were men and 27 (65.9%) were women, and their mean age was 77.8±7.89 (range, 65–95) years. In terms of the adequacy of the number of patients, power analysis was performed. We calculated the sample size according to the results of the seven patients in the study. From these differences and assuming a two-tailed α value of 0.05 (sensitivity 95%) and a β value of 0.20 (study power: 80%, effect size: 0.8), we determined that at least 30 patients were required for our study (G Power 3 power analysis programme) (9). We decided that we have enough patients for the study.

The mean durations of surgery, intensive care unit (ICU) stay, and hospitalization were 136.3±41.5 min, 1.2±2.4 days, and 8.2±2.7 days, respectively. The demographic and clinical characteristics of the patients are summarized in Table 1. The duration of ICU stay was positively correlated with the age of the patient (p=0.006, r=0.422) and the baseline NLR (p=0.018, r=0.368). Predictably, the duration of hospitalization was positively correlated with the duration of ICU stay (p=0.002, r=0.473).

Anesthetic technique

General, combined spinal-epidural, and spinal anesthesia were administered in 18 (43.9%), 13 (31.7%), 10 (24.4%) patients, respectively. Complications occurred in 25 (61%) of the patients during anesthesia or surgery; bleeding

Table 1. Baseline demographic and clinical characteristics of the patients

	n (%)
Gender	
Female	27 (65.9)
Male	14 (34.1)
Type of prosthesis	
Total	9 (22)
Partial	32 (78)
Type of anesthesia	
General	18 (43.9)
Spinal	10 (24.4)
Combined spinal-epidural	13 (31.7)
Complication	
Embolism	1 (2.4)
None	16 (39)
Bleeding	16 (39)
Hypotension	6 (14.6)
Delirium	2 (4.9)
Transfusion	
0	14 (34.1)
1	21 (51.2)
2	5 (12.2)
3	1 (24)

(39%) followed by hypotension (14.6%) were the most common complications. The prevalence of complications was lower in the spinal anesthesia group than in other groups. Moreover, the duration of ICU stay was the lowest in the spinal anesthesia group and highest in the general anesthesia group (p=0.016). Furthermore, the requirement for blood transfusion was the lowest in the spinal anesthesia group.

One-year mortality

Within one year after surgery, seven (30.6%) deaths were reported, including one patient who received spinal-epidural anesthesia and six patients who received general anesthesia (p=0.044; Table 2). In our study, in-hospital mortality occurred in only one patient who received general anesthesia because of postoperative pulmonary embolism. With regard to 1-year mortality, a significant difference was observed among the patients who received spinal, combined spinal-epidural anesthesia, and general anesthesia. NLR of >5.18 was determined to be the optimal cutoff level. The ROC curve analysis and the area under the ROC curve indicated a specificity of 85.7% and a sensitivity of 94.8% for the baseline NLR for predicting 1-year mortality. A significant association was observed between mortality and NLR on T2 (p=0.017) (Figure 2).

NLR

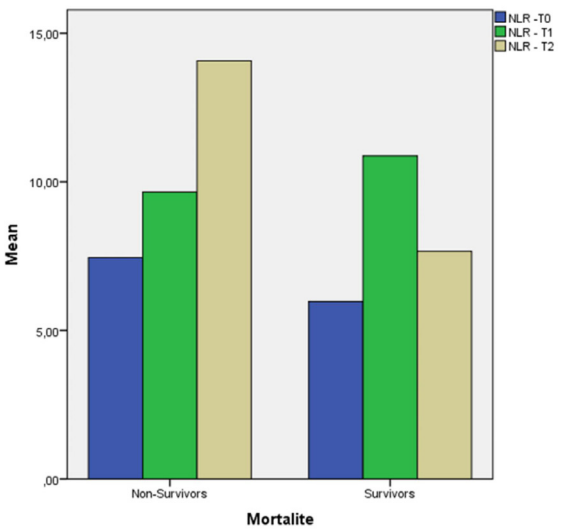
The baseline NLR (T0) was 6.22±3.8 and increased to 10.66±11.47 on T1 and 8.75±7.81 on T2. The increase in NLR from T0 to T1 (p=0.006) and the decrease from T1 to T2 (p=0.033) was statistically significant; however, no significant difference was observed in NLR between T0 and T2 (p=0,241). Moreover, no significant difference was observed in NLR between genders and types of prosthesis (p=0.142). However, a rapid increase in NLR on T2 was observed among the survivors and nonsurvivors (Figure 2).

Table 2. Mean Comparison of the demographic data between the surviving and non-surviving patients.

	Non- Surviving	Surviving	p
		Median (min-max) / n (%)	
Age (years)	75 (65-93)	80 (65-95)	0.245
Gender			
Female	4 (57.1%)	23 (67.6%)	0.594
Male	3 (42.9%)	11 (32.4%)	
Type of prosthesis			
Total	3 (42.9%)	6 (%17.6%)	0.142
Partial	4 (57.1%)	28 (82.4%)	
Anesthetic techniques			
General	6 (85.7%)	12 (35.3%)	0.044*
Spinal	-	10 (29.4%)	
Combined spinal-epidural	1 (14.3%)	12 (35.3%)	
Duration of surgery (min)	135 (100-260)	132.5 (55-240)	0.614

* Chi- square test

Figure 2. NLR values based on the survival status of 41 patients aged over 64 years following hip replacement surgery



No significant difference was found among the NLR values in each of the general anesthesia, spinal anesthesia, and combined spinal-epidural anesthesia groups (p=0.223, p=0.122, and p=0.292, respectively). However, a significant difference was found between general anesthesia and spinal anesthesia with regard to NLR values at T0, T1, and T2 (p=0.0013, p=0.0017, and p=0.004, respectively). Similarly, a significant difference was found between spinal anesthesia and combined spinal-epidural anesthesia with regard to NLR values at T1 (p=0.016) (Table 3). Furthermore, a positive correlation was observed between the baseline NLR and the duration of ICU stay (p=0.018; r=0.368).

DISCUSSION

In this study, we hypothesized that anesthetic techniques may have an effect on NLR and influence mortality rate in elderly patients with CAD who underwent hip replacement surgery. Our results showed that NLR on T2 was significantly higher in the general anesthesia group than in the spinal anesthesia group and that NLR predicted 1-year mortality. Moreover, a significant association was observed between mortality and NLR on T2; furthermore, NLR of >5.18 was determined to be an optimal cutoff level. To our knowledge, this is the first study investigating the effect of anesthetic techniques on NLR and mortality rates in elderly patients with CAD who underwent hip replacement surgery.

CVD is the most common cause of overall mortality in the general population (5,8). More than half of the patients who die because of CVD are aged ≥65 years. The prevalence of CAD, a major CVD, increases with age, particularly in the elderly population (8). CAD requires surgical intervention in half of the elderly patients aged ≥65 years. Furthermore, hip replacement surgery, which is associated with impaired mobility and increased morbidity and mortality in elderly patients, is prevalent is elderly patients with CAD (5). Therefore, an increasing number of elderly patients with CAD who undergo hip replacement surgery are encountered in anesthesia practice.

The "stress response" to surgery leads to the activation of the sympathetic nervous system and various endocrine, immunological, and hematological alterations, thereby resulting in adverse events such as increased oxygen consumption, hypertension, tachycardia, arrhythmia, myocardial ischemia, hemodynamic instability, catabolism, and immune dysfunction. Additionally, stress response has been associated with poor postoperative prognosis and clinical outcomes in patients with cardiovascular diseases, infection, and immunosuppression and in patients with a known diagnosis of endocrine, metabolic, and immune disorders (10, 11).

NLR provides information regarding the association between systemic inflammatory response and physiological stress (12). NLR, is a

Table 3. The effect of anesthetic techniques on NLR.

Anesthetic Technique	NLR T0	NLR T1	NLR T2	P*
	Mean ± SD	Mean ± SD	Mean ± SD	
General	7.33±3.67	14.79±15.70	11.89±9.67	0.223
Spinal	3.50±1.38	5.79±4.21	5.14±3.83	0.112
Combined spinal-epidural	6.77±4.39	8.70±5.16	7.18±5.83	0.292
P**	0.015a	0.021b	0.032c	

*Freidman test; ** Mann Whitney-U test (Kruskal-Wallis test was applied to non-parametric data with a 95% confidence interval and p level of <0.05 accepted significant. In the presence of a significant difference between the data sets, two groups were compared using Mann-Whitney U test to determine whether the differences between the groups were significant), a . Compared to general and spinal Anesthetic Technique (p = 0.0013) ,b. Compared to general and spinal Anesthetic Technique (p = 0.0017), Compared to spinal and combined spinal-epidural Anesthetic Technique (p = 0.016), c. Compared to general and spinal Anesthetic Technique(p = 0.004)

parameter indicating both elevation of neutrophils reflecting acute inflammatory response and reduced lymphocytes reflecting physiological stress. Moreover, NLR has been shown to be a simple predictive marker of clinical outcomes in patients with stable coronary artery disease (13).

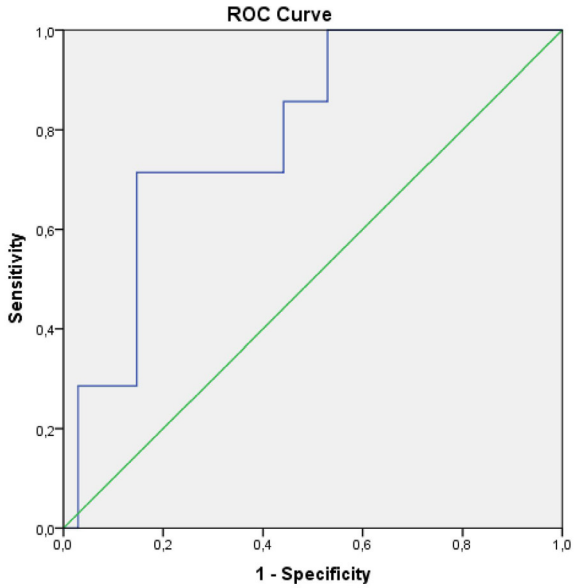
Pain, anesthesia, and surgery are the major stresses in elderly patients with HF. NLR may reflect the persistent status of stress in elderly patients because of The stress-induced hormonal changes involve cortisol secretion, which increases the number of neutrophils through vascular demargination and decreases the number of lymphocytes through a possible central medullary effect (3).

A systematic review by Tan et al. discussed the effects of NLR on mortality and morbidity in patients undergoing cardiovascular surgery (14). The results of the study confirmed a known association between increased NLR and increased mortality following myocardial infarction, chronic ischemic heart disease, and percutaneous coronary intervention. In another study, NLR was shown to be significantly increased in elderly patients with acute myocardial infarction compared with their younger spouses (<60 years); NLR of 9.41 was accepted as the optimal cutoff value for predicting in-hospital mortality (15).

The reduction and modulation of the stress response to surgery is associated with significantly decreased postoperative complications and morbidity. However, this achievement is largely dependent on the choice of an ideal anesthetic technique. Accordingly, previous studies indicated that the choice of anesthetic technique affects intraoperative stress response and thus has a significant effect on the clinical outcomes, morbidity, and the reduction of postoperative pain in patients undergoing surgical treatment. In turn, the choice of anesthetic technique is dependent on various factors including the characteristics of the disease, general condition of the patient, type and severity of the surgical procedure, and the availability of anesthetic equipment and services (10).

NLR is affected not only by the stress response to surgery but also by the choice of anesthetic technique. The formed responses are affected by factors such as direct pharmacological effect of anesthetic material and the type, duration and depth of anesthesia. The neuroendocrine alterations caused by anesthetic techniques are known to affect NLR and to have an indirect effect on postoperative complications; therefore, they are likely to affect the choice of anesthetic technique (16).

Figure 3. Performance analysis of NLR for one-year mortality in 41 patients aged over 64 years following hip replacement surgery. The area under the curve (AUC) for the NLR at T2 was 0.79 [95% CI, 0.625–0.955] (p=0.017, AUC=0.79) with an optimal cut-off value of 5.18. (specificity 85.7% ,sensitivity 94.8%)



The effects of general and regional anesthesia on proinflammatory and anti-inflammatory cytokines have been extensively shown in previous studies. (17, 18)Regional anesthesia has been shown to have several advantages over general anesthesia such as inhibition of metabolic and hormonal responses to surgery, reduced incidence of postoperative pain, accelerated peristalsis following abdominal surgery, reduced incidence of deep vein thrombosis, and shorter hospitalization periods. These advantages are attributed to spinal anesthesia blocking the sensory afferent nerve impulses originating from the surgical trauma and also to the blocking of the efferent and afferent pathways of the sympathetic and somatic nervous system that inhibits activation of the neuroendocrine axis during surgical procedures (10).

Our knowledge, no comprehensive study has reported regarding the effects of inhaled, spinal, or combined spinal-epidural on NLR in elderly patients undergoing specific surgeries. There are only limited studies regarding the effect of anesthetic techniques on NLR (16, 18-19). A previous retrospective study evaluating the relationship between NLR and the choice of anesthetic technique in patients undergoing cesarean section and reported that the postoperative NLR values were significantly lower in patients that underwent spinal anesthesia compared to general anesthesia (18). Another study evaluated the relationship between NLR and the choice of anesthetic technique in patients undergoing infraumbilical surgery and revealed that both postoperative total leukocyte count and NLR values were significantly higher in patients that underwent general anesthesia compared to spinal anesthesia (16). In our study, NLR in all time periods was significantly higher in the general anesthesia group than in the spinal anesthesia group.

In a retrospective analysis of 247 patients aged >65 years who had undergone surgery for HF, Forget et al. evaluated 1-year mortality based on perioperative NLR. General anesthesia was administered in most patients (98.4%), and the results indicated that NLR measured at postoperative day 5 was a risk factor for postoperative mortality and cardiovascular complications (3). Another study by the same authors estimated the mortality score in elderly patients with HF using a discrete 0–4 scoring system based on NLR and an NLR cutoff value of 4.9. The authors concluded that the scoring system could predict mortality in elderly patients within the first year after surgery. Nevertheless, details regarding the anesthetic technique used in the study were unavailable (20).

Fisher et al. examined the short-term outcomes of NLR in orthogeriatric patients and observed significant associations among the presence of

HF, postoperative complications, and NLR. NLR of >5.1 was associated with an increased risk of fractures, developing postoperative myocardial injury (troponin I increase), and a high inflammatory response/infection (21). Moreover, NLR of ≥5.1 and >8 could predict postoperative myocardial injury and in-hospital mortality, respectively. However, details regarding the anesthetic technique used in the study were unavailable.

In our study, the NLR cutoff value was 5.18, which was similar to that in previous studies (3,20). However, the increased NLR on T2 was revealed to be a prognostic factor for 1-year mortality. Furthermore, the incidence of 1-year mortality was observed to be higher in patients receiving general anesthesia than in those receiving other types of anesthesia; the lowest mortality rate was observed in the spinal anesthesia group. Similarly, the effect of spinal anesthesia on NLR on T2 was lower than that of general anesthesia.

Our study is a retrospective analysis of single-center for this reason a limitation of our study was the nonhomogeneous study design with regard to patients' ages associated with an increased risk of mortality (i.e., 65–95 years). Another limitation was that the study did not provide information regarding the nutritional status of the patients, although malnutrition is known to be a risk factor following HF and is typically associated with lymphopenia. Therefore, there is no nutritional data and it has been excluded from the scope of the study.

In conclusion, our study indicated that NLR measured on T2 and general anesthesia are associated with a high risk of mortality in elderly patients with CAD who underwent surgery for HF. Moreover, spinal anesthesia was observed to be associated with a lower mortality rate by minimizing NLR value on T2 than general anesthesia.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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RESEARCH

EFFECT OF AGE ON ANASTOMOTIC LEAKAGE AND RELATED MORTALITY FOLLOWING COLORECTAL CANCER SURGERY

Abstract

Purpose: The present study aimed to investigate the correlation between age and anastomotic leakage and leak-related mortality following colorectal cancer surgery.

Material and Method: Data of patients who underwent elective resection and anastomosis for colorectal cancer between January 2013 and December 2018 were retrospectively evaluated. Patients were divided into two groups: patients aged <65 years (Group 1) and those aged ≥65 years (Group 2). Demographic characteristics, perioperative risks, diseased colonic segment, neoadjuvant chemoradiotherapy and surgical procedure (laparoscopic/open) were evaluated between both groups. The primary endpoint of the study was the development of anastomotic leakage within 30 days postoperatively. The secondary endpoint was the leak-related mortality within 30 days postoperatively.

Results: The study included 358 patients; 60.6% of these were male and 39.4% were female, and mean age was 65.9 ± 12.33 years. The rate of anastomotic leakage was 5.6% (n = 9) in Group 1 and 5.1% (n = 10) in Group 2 (p = 0.283). Overall leak-related mortality was 1.95%. The leak-related mortality was 0.6% in Group 1 and 3.06% in Group 2 (p = 0.043).

Conclusion: Our results demonstrate that age is not a risk factor for anastomotic leakage following colorectal cancer surgery; however, there is an increased mortality following anastomotic leakage in elderly patients.

Keywords: Anastomotic leakage; Aged; Colorectal cancer; Mortality

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ARAŞTIRMA

YAŞIN KOLOREKTAL KANSER CERRAHİSİ SONRASI ANASTOMOZ KAÇAĞI VE BUNA BAĞLI GELİŞEN MORTALİTE ÜZERİNE ETKİSİ

Öz

Amaç: Kolorektal kanser cerrahisi sonrası oluşan anastomoz kaçağının ve buna bağlı gelişen mortalitenin yaş ile ilişkisini araştırmaktır.

Materyal ve Metod: Ocak 2013-Aralık 2018 tarihleri arasında kolorektal kanser nedeniyle elektif şartlarda rezeksiyon ve anastomoz yapılan hastaların verileri retrospektif olarak değerlendirildi. Hastalar, <65 yaş (Grup 1), ≥65 yaş (Grup 2) olmak üzere iki gruba ayrıldı. Hastaların demografik özellikleri, perioperatif riskler, hastalıklı kolon segmenti, neoadjuvan kemoradyoterapi alıp almaması ve uygulanan cerrahi prosedür (laparoskopik/açık) iki grup arasında irdelendi. Çalışmanın birinci sonuç ölçütü ameliyattan sonra 30 gün içerisinde gelişen anastomoz kaçağı idi. İkinci çalışma ölçütümüz ise postoperatif 30 gün içerisinde anastomoz kaçağına bağlı gelişen mortalite idi.

Bulgular: Çalışmaya 358 hasta dahil edildi. Hastaların %60.6'sı erkek, %39.4'ü kadın idi ve yaş ortalamaları 65.9±12.33 idi. Anastomoz kaçağı oranı Grup 1'de %5.6 (n=9), Grup 2'de %5.1 (n=10) olarak saptandı (p=0.283). Anastomoz kaçağına bağlı gelişen toplam mortalite %1.95 idi. Grup 1'de anastomoz kaçağına bağlı mortalite %0.6 iken Grup 2'de %3.06 idi (p=0.043).

Sonuç: Kolorektal kanser cerrahisi sonrası yaşın anastomoz kaçağı için risk faktörü olmadığını ancak anastomoz kaçağı sonrası mortalitenin ileri yaşlı hastalarda arttığını göstermektedir.

Anahtar sözcükler: Anastomoz kaçağı; Yaşlı; Kolorektal kanser; Mortalite

INTRODUCTION

Colorectal cancer ranks third among all cancers (1). The elderly population has significantly increased in recent years, and advanced age is a risk factor for the development of colorectal cancer (2). This increase is expected to continue owing to the initiatives toward increasing life expectancy and early diagnosis (3,4). Of the patients diagnosed with colorectal cancer, 50% are aged ≥60 years and postoperative mortality and morbidity is high in elderly patients owing to the presence of comorbid diseases (5). However, curative resection is the main treatment for colorectal cancer. Studies have shown that advanced age is not a contraindication for colorectal cancer surgery (CCS) and that CCS can be safely performed and overall survival is similar to life expectancy (6,7). Although the cause remains unclear, anastomotic leakage (AL) that develops following colorectal surgery is one of the major complications that is worrisome because of the increased morbidity and mortality as well as of their negative impact on the duration of hospital stay and functional and oncologic outcomes. However, studies investigating this subject in elderly patients are limited in literature. Whether age plays a role in AL remains a matter of debate. Gessler B et al. have reported that AL does not correlate with age (8). Ureyen O et al. have reported that the risk of AL is higher in the elderly population (9). In contrast, Park JS et al. have reported that AL is more common in the young population (10). Following colorectal surgery, AL is observed in 3%–28% of cases and is responsible for one-third of postoperative mortality (11). However, AL-related mortality is higher in elderly patients (12). Unfortunately, there is a paucity of data on this subject in literature. The present study aimed to investigate the relationship between age and AL and AL-related mortality following CCS.

MATERIALS AND METHOD

Study design

Data of patients who underwent elective resection and anastomosis for colorectal cancer in our clinic between January 2013 and December 2018 were retrospectively evaluated by reviewing the hospital database system and patient files. The present study was approved by the ethics committee of our hospital (2019/514/148/13).

Patients who did not undergo curative resection for colorectal cancer, those treated with Hartmann procedure or transanal local resection, those treated only with deflective stoma, those with missing data, and those who were operated under emergency conditions were excluded from the study. According to the American Joint Commission on Cancer (AJCC) TNM staging (13), patients with middle and lower rectal carcinoma other than T1 received neoadjuvant chemoradiotherapy (CRT) and total mesorectal excision was performed 8–10 weeks after CRT. A protective ileostomy was routinely performed following anastomosis below the peritoneal reflection in patients with rectal tumor who received neoadjuvant CRT. The decisions were made on a case-by-case basis for the remaining patients with upper rectal and colonic tumors considering their general condition and depending on technical issues encountered both during anastomosis and during the perioperative period. In our study, all patients who underwent surgery for colorectal cancer under elective conditions underwent resection and anastomosis with or without stoma.

Outcome measure and other variables

Patients included in the study were divided into two groups: patients aged <65 years (Group 1) and those aged ≥65 (Group 2). Demographic characteristics, perioperative risks, diseased colonic segment, neoadjuvant CRT, and surgical procedure (laparoscopic/open) were evaluated between both groups. The primary endpoint of the study was AL that developed within 30 days postoperatively. The secondary endpoint was AL-related mortality within 30 days postoperatively.

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, New

York, United States) software was used for the analysis of variables. Descriptive data were presented as percentages, mean ± standard deviation. Normality testing (Kolmogorov Sminov) was performed to determine whether the data followed a Gaussian distribution or not. Continuous variables in two independent groups were compared with Student t test or the Mann-Whitney U test. Categorical variables were compare by Pearson's chi-square test or Fisher's exact test. A binary logistic regression analysis was performed to identify potentially risk factors for age groups. A p value < 0.05 was considered as statistically significant.

RESULTS

Study population

The study included 358 patients who underwent elective resection and anastomosis for colorectal cancer. Of these patients, 60.6% were male, 39.4% were female, and mean age was 65.9 ± 12.33. Tumors were most commonly localized in the rectum (23.7%) and sigmoid colon (23.7%).

Anastomotic leakage

Overall incidence of AL in the study group was 5.3% (n = 19). The rate of AL was 5.6% (n = 9) in Group 1 and 5.1% (n = 10) in Group 2 (p = 0.283). Age was not found to have a significant influence on the development of AL. Of the 19 patients that developed AL, 9 had stoma and 10 had no stoma (p = 0.78).

When patient files and database were reviewed for the treatment and management of the patients with AL, of 9 patients with protective stoma that developed AL, 3 were detected, on an average, on the 5th day of the postoperative follow-up period (4-7) and 6 were detected when they presented to the General Surgery outpatient clinic with symptoms of abdominal pain and fever on average on the 11th day after discharge from the hospital (7-19). Conversely, in all patients without protective stoma that developed AL, diagnosis was made by means of clinical observation and imaging methods on the 4th day (3-7) of their postoperative follow-up period. Only two patients with protective stoma who developed AL required relaparotomy after the first operation. Of these 9 patients, 3 died in the postoperative period, 4 underwent ileostomy closure without any problems after completion of oncological treatment, and in the remaining 2 patients with anastomotic stricture, ileostomy was not closed in 1 patient and the other patient underwent the Hartmann procedure after ileostomy closure owing to acute renal failure. It was observed that relaparotomy was required in 8 out of 10 patients without protective stoma that developed AL. Of these patients, 6 underwent Hartman procedure and 2 underwent ileostomy operation. Endoscopic clipping was performed in 2 patients who did not require relaparotomy and showed no evidence of peritonitis on physical examination.

Mortality

Overall mortality was 0.6% (n = 1) in Group 1 and 4.1% (n = 8) in Group 2 (p = 0.037). AL-related mortality occurred in only one patient in Group 1, whereas it occurred in 6 out of 8 patients in Group 2. Of these 6 patients, protective stomas were performed in 3 patients, whereas it was not performed in the remaining 3. The total AL-related mortality was 2%; AL-related mortality was 0.6% in Group 1 and 3.1% in Group 2 (p = 0.043).

According to age groups, in favor of advanced age group hypertension, congestive heart failure (CHF), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), high American Society of Anesthesiologists (ASA) score, and presence of protective stoma found statistically significant (Table 1). There was a significant difference between both groups in terms of tumor N stage, number of lymph nodes removed, and number of metastatic lymph nodes (Table 2). Binary logistic regression analysis showed that CHF, CAD, presence of protective stoma, high ASA score, and number of metastatic lymph nodes significantly correlated with age (Table 3).

Table 1. Clinical characteristic of patients according to age groups.

		Group 1 (<65 years) n(%)	Group 2 (≥65 years) n(%)	Total n(%)	p
Age (average ± sd.)		54.52 ± 6.03	75.11 ± 7.46	65.79 ± 12.33	0.001**
Sex	Female	55(34.0)	86(43.9)	141(39.4)	0.056*
	Male	107(66.0)	110(56.1)	217(60.6)	
ASA(average ± sd.)		2.29 ± 0.46	2.81 ± 0.40	2.57 ± 0.49	0.001**
Anastomotic leakage	No	153(94.4)	186(94.9)	339(94.7)	0.283*
	Yes	9(5.6)	10(5.1)	19(5.3)	
Tumor location	Ascending Colon	23(14.2)	31(15.8)	54(15.1)	0.849*
	Descending Co-lon	0(0.0)	9(4.6)	9(2.5)	
	Rectosigmoid	41(25.3)	35(17.9)	76(21.2)	
	Rectum	47(29)	38(19.4)	85(23.7)	
	Sigmoid	24(14.8)	53(27)	77(21.5)	
	Splenic Flexure	1(0.6)	0(0.0)	1(0.3)	
	Transverse Co-lon	26(16)	30(15.3)	56(15.6)	
Protective ileostomy	No	126(77.8)	171(87.2)	297(83.0)	0.018*
	Yes	36(22.2)	25(12.8)	61(17.0)	
Mortality	No	161(99.4)	188(95.9)	349(97.5)	0.037*
	Yes	1(0.6)	8(4.1)	9(2.5)	
Intestinal preparation	No	0(0.0)	2(1)	2(0.6)	0.197*
	Yes	162(100.0)	194(99.0)	356(99.4)	
Comorbidity	Diabetes	35(21.6)	53(27.0)	88(24.6)	0.234*
	Hypertension	31(19.1)	103(52.6)	134(37.4)	0.001*
	Heart Failure	3(1.9)	31(15.8)	34(9.5)	0.001*
	MI	3(1.9)	0(0.0)	3(0.8)	0.056*
	COPD	6(3.7)	20(10.2)	26(7.3)	0.018*
	CAD	2(1.2)	17(8.7)	19(5.3)	0.002*
	CKF	4(2.5)	9(4.6)	13(3.6)	0.285*
Blood Transfusion	No	133(82.1)	148(75.5)	281(78.5)	0.131*
	Yes	29(17.9)	48(24.5)	77(21.5)	
Operation technique	Laparoscopic	46(28.4)	40(20.4)	86(24.0)	0.078*
	Open	116(71.6)	156(79.6)	272(76.0)	

*Chi-square test (Fisher's exact test). ** Mann–Whitney U analysis.Sd: Standard deviation.

ASA: American Society of Anesthesiologists, MI: Myocardial infarction, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CKF: Chronic kidney failure.

DISCUSSION

The number of people aged ≥60 and is estimated to exceed 2 billion by 2050 (14). There is no consensus on the age limit in the definition of the elderly (15). The threshold of 65 years used in our study was in accordance with the elderly definition of the World Health Organization, although it would not completely reflect the physical decline associated with advanced age (16). Advanced age is a risk factor for the development of colorectal cancer, in addition to being the most important risk factor for postoperative mortality and morbidity (5). With increasing elderly population, there is an emerging need of recognizing specific risks associated with surgery (17). However, studies conducted to date have not adequately addressed the relationship between age and AL, which is one of the most serious complications of colorectal surgery, and AL-related morbidity and mortality. In the present study, we aimed to investigate the relationship between age and AL, as well as AL-related mortality, following CCS performed under elective conditions.

It has been reported that 50% of the patients diagnosed with colorectal cancer are aged ≥60 years (5). In our study, elderly patients constituted 54.7% of the study sample. In literature, male sex, high ASA score, CAD, COPD, steroid use, and diabetes mellitus have been reported as independent risk factors for AL (15,18). In our

Table 2. TNM stage, number of lymph nodes excised and neoadjuvant CRT in the groups.

		Group 1 n(%)	Group 2 n(%)	Total n(%)	p
T stage	T0	3(1.9)	3(1.5)	6(1.7)	0.512*
	T1	22(13.6)	20(10.2)	42(11.7)	
	T2	106(65.4)	143(73.0)	249(69.6)	
	T3	6(3.7)	3(1.5)	9(2.5)	
	T4	25(15.4)	27(13.8)	52(14.5)	
N stage	N0	74(45.7)	109(55.6)	183(51.1)	0.048*
	N1	41(25.3)	51(26)	92(25.7)	
	N2	47(29)	36(18.4)	83(23.2)	
TNM stage	<3	72(44.4)	105(53.6)	177(49.4)	0.359*
	≥3	90(55.6)	91(46.4)	181(50.6)	
Neoadjuvant therapy	No	120(74.1)	160(81.6)	280(78.2)	0.085*
	Yes	42(25.9)	36(18.4)	78(21.8)	
Number of lymph nodes removed(average ± sd.)		19.77± 8.99	17.56 ± 9.30	18.56 ± 9.21	0.024**
Number of metastatic lymph nodes(average ± sd.)		3.45 ± 5.90	1.79 ± 2.90	2.54 ± 4.58	0.001**

* Chi-square test (Fisher's exact test)** Mann–Whitney U analysis.
CRT: Chemoradiotherapy, TNM;T: Tumor, N: Node, M: Metastasis.

Table 3. Binary logistic regression analysis of according to the ages groups.

Variables	Odds ratio	95% CI	p value
Preventive ileostomy	5.893	2.631 to 13.199	0.001
ASA	9.439	4.639 to 19.206	0.001
CAD	0.229	0.043 to 1.210	0.043
Heart failure	0.082	0.021 to 0.326	0.001
Number of metastatic lymph node	0.875	0.777 to 0.985	0.028
Mortalite	0.153	0.0002 to 0.111	0.006

CI: Confidence Interval.Compared to general and spinal Anesthetic Technique (p = 0.0017), Compared to spinal and combined spinal-epidural Anesthetic Technique (p = 0.016), c. Compared to general and spinal Anesthetic Technique(p = 0.004)

study, binary logistic regression analysis showed that CHF, CAD, high ASA score, and number of metastatic lymph nodes significantly correlated with advanced age. Although these predictive factors related to AL are more significant in elderly patients, it is a matter of debate whether age plays a role in AL development. In the study by the Danish Colorectal Cancer Group and the American College of Surgeons National Surgical Quality Improvement Program, increasing age has been reported to correlate with a decrease in the rate of AL (19). They attributed this finding to both more meticulous preoperative preparation and surgical intervention in the elderly patients. In contrast to these findings, another study has reported an increasing incidence of AL with increasing age (20). In a meta-analysis of 16 studies involving a total of 4,479 cases, no significant difference was reported between the elderly and young patients in terms of the risk of developing AL (21).

The rate of AL following colon resection due to benign and malignant causes is 3.0%–6.4% (22,23). Rencuzogulları et al. have studied a cohort of 10,392 cases aged >65 years that underwent colon resection due to benign and malignant causes and reported that the rate of AL was 3.2% (15). In 45,488 patients who underwent surgery for colorectal cancer, Zaimi et al. have reported an incidence of 6.4% for AL in patients aged <60 years, 5.5% in patients aged 60–69 years, 5.4% in patients aged 70–80 years, and 4.9% in patients aged ≥80years (12).

In our study, the overall AL incidence was 5.3% (n = 19) in patients who underwent elective surgery for colorectal malignancy. The rate of AL was found to be 5.6% (n = 9) in patients aged <65 years and 5.1% (n = 10) in those aged ≥65 years. Age was not a significant factor for the development of AL. Of the 19 patients that developed AL, stoma was performed in 9 and it was not performed in 10 (p = 0.780). In the present study, we found that stoma had no protective effect against AL. This result was consistent with that observed previously (24).

Effective treatment is essential when AL is diagnosed. Early decision of surgery is the most important factor that reduces mortality. Especially AL, which develops in patients with protective stoma, is mostly asymptomatic, and medical supportive therapy is often sufficient. In patients with extraperitoneal anastomosis who do not have signs of peritonitis during examination, special drains inserted into the fistula tract following endoscopic debridement and negative-pressure

aspiration facilitate healing in AL and reduce the need for a second surgical intervention (8). In cases without protective stoma, proximal fecal diversion can be performed, and in cases with extensive peritonitis and those in which anastomosis is fully separated, the Hartmann procedure is essential (8). Of 9 patients with protective stoma included in this study, 2 were followed up with an endosponge, 4 with percutaneous drainage, 1 with stent, and 2 with only medical therapy. Of 10 patients without protective stoma that developed AL, relaparotomy was performed in 8 patients, 6 of whom underwent the Hartman procedure and 2 underwent ileostomy construction. Endoscopic clips were placed in the other 2 patients.

AL following colorectal surgery is responsible for one-third of postoperative mortality (11). However, AL-related mortality is higher in elderly patients (12). A multicenter study has reported four times higher mortality following AL in elderly patients compared with young patients (25). In the study by Zaimi et al., mortality following AL in patients who underwent surgery for colorectal cancer was reported to be 1.3% in patients aged <60 years, 4.8% in patients aged 60–69 years, 12.3% in patients aged 70–80 years, and 27.0% in patients aged ≥80 years (12).

In our study, the overall AL-related mortality was 1.95%. AL-related mortality was 0.6% in patients aged <65 years and 3.06% in patients aged ≥65 years ($p = 0.043$). In our study, patients aged ≥65 years exhibited higher number of comorbidities. This was related to the high ASA score of the elderly patients ($p = 0.001$). The significant difference between mortality of the two groups can be attributed to comorbidities in elderly patients; moreover, not consenting to a second surgery following AL is a possible reason. In our study, protective stoma was more common among the patients aged <60 years. This is attributable to the higher number of patients with rectal and rectosigmoid localization in this group compared with that in the group of patients ≥60 years.

In our clinic, post-anastomosis protective ileostomy below the peritoneal reflection is routinely performed in patients with rectal tumor receiving neoadjuvant CRT. The decision is made on a case-by-case basis for the remaining patients with upper rectal and colonic tumors considering their general condition and depending on technical issues encountered both during anastomosis and during the perioperative period. Protective stomas do not reduce the occurrence of AL; however, they reduce the severity of AL-related septic findings and facilitate the treatment of leakages using palliative methods (24).

The reason for low mortality in our study compared with that reported in literature is that the studies in the literature are heterogeneous studies including patients operated under both emergency and elective conditions. However, our study consisted of patients who were operated under elective conditions involving preoperative preparation. We believe that this difference allowed us to obtain more significant results compared to other studies.

In our study, higher ASA score was observed in elderly patients, and AL-related mortality was significantly higher in these patients. It has been shown that laparoscopic surgery for colorectal cancer is as safe in elderly patients as it is in younger patients (21). Our results are consistent with those in the literature. In our study, right hemicolectomy due to right-sided colon-localized tumor exhibited the lowest rate of AL in both groups. The incidence of AL was mostly observed in surgeries related to rectum-localized tumors.

In conclusion, the present study shows that age is not a risk factor for AL following CCS; however, there is an increase in AL-related mortality in elderly patients.

CONFLICT OF INTEREST

All authors declare that there is not any conflict of interest.

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RESEARCH

EVALUATION OF TEAR FILM LAYER AND MEIBOMIAN GLAND MORPHOLOGY IN GERIATRIC PATIENTS WITH CHRONIC BLEPHARITIS

Abstract

Introduction: To investigate the changes in meibomian gland morphology and their effects on tear parameters in geriatric patients with chronic blepharitis.

Materials and Method: The study included 70 eyes of 35 healthy subjects in the control group and 60 eyes of 30 patients with chronic blepharitis. The patients were requested to complete a symptom questionnaire [Ocular surface disease index] before clinical examination. Non-contact meibography and non-invasive tear break-up time tests were performed with the Sirius Scheimpflug camera. Meibography scoring (Meiboscore) of the upper and lower lids was performed in all patients. Invasive tear break up time was performed 1 min after putting a single drop of fluorescein in all patients.

Results: The mean age of the patients was 74.6±7.1 and 73.9±6.3 years in the blepharitis and control groups, respectively (p = 0.669). The total meiboscore, non-invasive first and mean tear break up time, invasive tear break up time, and ocular surface disease index score were 3.6±1.7, 8.0±4.8, 9.7±4.0, 7.1±3.0, and 27.4±11.7, respectively, for the blepharitis group and 3.0±1.4, 10.4±5.7, 11.4±5.0, 8.6±3.1, and 18.0±6.4, respectively for the control group (respectively p = 0.03, 0.01, 0.03, 0.00, 0.00).

Conclusion: Chronic blepharitis in patients aged ≥65 years was associated with morphological changes in meibomian gland, decreased tear break up time, and increased ocular surface disease index scores. In these patients, meibomian gland atrophy score is considered as a valuable method consistent with clinical findings.

Keywords: Blepharitis; Tears; Dry eye syndromes; Meibomian gland; Aged

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ARAŞTIRMA

KRONİK BLEFARİTLİ GERİATRİK HASTALARDA MEİBOMİAN BEZ MORFOLOJİSİ VE GÖZ YAŞI FİLM TABAKASININ DEĞERLENDİRİLMESİ

Öz

Giriş: Bu çalışmada kronik blefariti olan geriatrik hastalarda meibomian bez morfolojisini ve bunun gözyaşı parametrelerine olan etkisini değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya 30 kronik blefaritli hastanın 60 gözü ve kontrol grubuna 35 sağlıklı bireyin 70 gözü dahil edildi. Klinik muayene öncesinde tüm hastalardan semptom anketini tamamlaması istendi [Oküler yüzey hastalık indeksi]. Non-kontakt meibografi ve non-invaziv göz yaşı kırılma zamanı ölçümleri Sirius Scheimpflug Camera ile yapıldı. Tüm olgularda her iki gözde alt ve üst kapaklarda meibografi skorlaması (Meiboskor) yapıldı. Tüm olgularda invaziv gözyaşı kırılma zamanı bir damla floresein damlatıldıktan 1 dakika sonra ölçüldü.

Bulgular: Çalışmaya alınan olgularda yaş ortalaması blefarit grubunda 74.6±7.1, kontrol grubunda 73.9±6.3 yıldı (p = 0.669). Sırasıyla toplam meiboskor, non-invaziv ilk ve ortalama gözyaşı kırıma zamanı, invaziv gözyaşı kırılma zamanı, oküler yüzey hastalık indeksi skoru blefarit grubunda 3.6±1.7, 8.0±4.8, 9.7±4.0, 7.1±3.0, 27.4±11.7 iken kontrol grubunda 3.0±1.4, 10.4±5.7, 11.4±5.0, 8.6±3.1, 18.0±6.4 bulundu (sırasıyla p = 0.03, 0.01, 0.03, 0.00, 0.00).

Sonuç: Altmışbeş yaş ve üzerindeki kronik blefaritli hastalarda meibomian bezlerde morfolojik değişiklikler, azalmış gözyaşı kırılma zamanı ve artmış oküler yüzey hastalık indeksi skorları olduğu görülmektedir. Bu hastalarda, meibomian bez atrofi skorunun klinik bulgularla uyumlu değerli bir yöntem olduğu düşünüldü.

Anahtar sözcükler: Blefarit, Gözyaşı, Kuru göz sendromu; Meibomian bez, Yaşlı

INTRODUCTION

Blepharitis is one of the common diseases encountered by ophthalmologists and can be defined as a large group of diseases that lead to the inflammation of the eyelid margin and ocular surface and can affect children and adults (1,2). The symptoms associated with this inflammatory condition are burning, irritation of the eyelid, crusting, and injection of the eyelid margin and conjunctiva. The exact cause of blepharitis is unknown, thereby making this condition difficult to treat (3).

Blepharitis is categorized in two different ways by Lindsley et al. (4). The first categorization is based on the disease duration: acute or chronic blepharitis. The second categorization is based on the anatomical position of the disease: anterior and posterior blepharitis. Notably, posterior blepharitis is more common and often involves the meibomian gland (MG) on the internal surface of the eyelid. Prolonged obstruction of the MG results in inflammation and hyperkeratinization of the ductal epithelium. Therefore, meibomian gland dysfunction (MGD) is thought to be a complication of posterior blepharitis (5).

MG provides the oily components of the tear film, which helps to reduce tear fluid evaporation. MGD is one of the most common causes of evaporative dry eye disease (DED), which is more common than the aqueous-deficient dry eye. Changes in MG morphology can be seen in patients with DED. MGD is a chronic condition, commonly characterized by duct obstruction or changes in the glandular secretion. The International Workshop on MGD defines "MGD as a chronic, diffuse abnormality of MG that is commonly characterized by terminal duct obstruction or qualitative or quantitative changes in glandular secretion" (6). Changes in the lipid composition of glandular secretion because of MGD result in instability of the tear film lipid layer, a common finding in ophthalmology practice. This situation leads to ocular surface disease symptoms. Non-invasive meibography helps to evaluate the status of MG in vivo, and owing to this method, the structure of MG, including channels and acini, can be completely observed. Additionally, non-invasive meibography provides photographic documentation of MG (7,8).

Conversely, the prevalence of DED has increased (9). The Asia Dry Eye Society recently reviewed the criteria for dry eye diagnosis and defined DED as follows: "dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage." This new definition emphasized the significance of the tear film in DED as well as the diagnostic importance of non-invasive meibography and tear film break-up time (TBUT) tests (10).

Several studies have shown that MGD increases with age (11-13). In addition, a study by McCann et al. (3) revealed a significant difference in tear physiology and MG function between patients with blepharitis and healthy individuals.

These reasons may point to a significant correlation between aging, blepharitis, MGD, and DED. Therefore, the present study investigated the MG morphology and its effect on the tear film layer in geriatric patients with chronic blepharitis.

MATERIALS AND METHOD

This study included 60 eyes of 30 patients with chronic blepharitis and 70 eyes of 35 healthy subjects in the control group. All patients were ≥65 years. Before the clinical examination, the patients were requested to complete a symptom questionnaire [ocular surface disease index scores (OSDI)]. This questionnaire gives a range of 0 (no symptoms) to 100 (severe symptoms). Non-contact meibography and non-invasive TBUT tests were performed using Sirius Scheimpflug camera (Costruzione Strumenti Ophthalmic, Florence, Italy). Non-invasive TBUT was automatically

detected with Sirius Scheimpflug camera (Figure 1). The first and mean non-invasive TBUT were recorded. The non-invasive TBUT measurements were performed first based on the assumption that the use of fluorescein drops in patients may affect TBUT duration. Thereafter, invasive TBUT was performed 1 min after a single drop of fluorescein was used in all patients. The invasive TBUT was evaluated using a slit lamp with a cobalt blue exciter filter. The first invasive TBUT was recorded. Finally, non-invasive meibography was performed in all patients. The lipids could be discharged from the MG orifices to the ocular surface by manipulating the lid during non-invasive meibography. This manipulation could have led to errors in TBUT measurement. Therefore, non-invasive meibography was performed after TBUT measurements. Meibography scoring (meibomian gland atrophy score or meiboscore) in the upper and lower lids of both the eyes was performed for all patients. First, MG of the upper eyelid was examined and graded. The grading was based on the criteria proposed by Arita et al. (7,11), where in the atrophy is graded as follows: 0 point for no atrophy, 1 point for less than one-third atrophy, 2 points for more than one-third atrophy,

Figure 1. Sirius Scheimpflug camera imaging in a representative patient; non-invasive first and mean tear film break-up time.

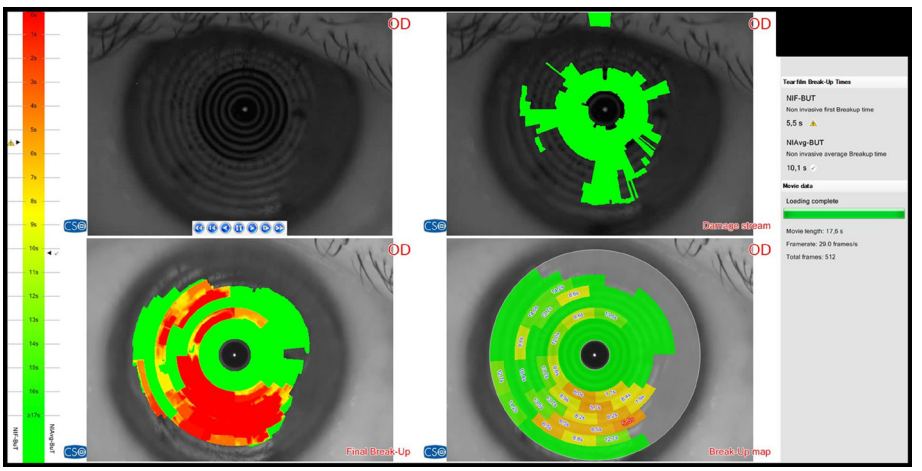
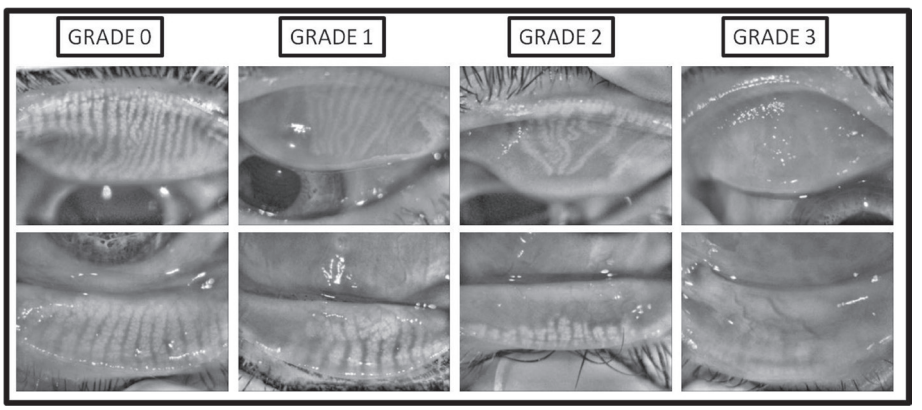


Figure 2. Non-contact meibography grading.



and 3 points for more than two-third atrophy. All eyelids were examined and graded in the same way (Figure 2). The values obtained for the upper and lower eyelids were then added to the total meiboscore ranging from 0–6. Patients who were <65 years; using contact lens; undergoing eyelid surgery; or having rosacea, glaucoma, chronic ocular disease, eyelid abnormalities, and systemic disease with dry eyes were excluded from the study. The control group included subjects over 65 years of age who had no ocular and systemic disease and had no ocular surgery.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). Normal distribution was assessed using the Kolmogorov–Smirnov test. Independent samples t-test was used to test the statistical significance, and a p value of <0.05 was considered statistically significant.

RESULTS

The blepharitis group comprised 22 women and 8 men, and the control group comprised 28 women and 7 men. The mean age of the patients included in the study was 74.6 ± 7.1 and 73.9 ± 6.3 years in the blepharitis and control group, respectively. No statistically significant difference was found regarding age and sex between the groups ($p = 0.669$).

Total meiboscore value was 3.6 ± 1.7 and 3.0 ± 1.4 for the blepharitis and control group, respectively ($p = 0.03$); non-invasive first TBUT duration was 8.0 ± 4.8 and 10.4 ± 5.7 sec ($p = 0.01$); non-invasive mean TBUT duration was 9.7 ± 4.0 and 11.4 ± 5.0 sec ($p = 0.03$); invasive TBUT duration was 7.1 ± 3.0 and 8.6 ± 3.1 sec ($p = 0.00$); and OSDI score was 27.4 ± 11.7 and 18.0 ± 6.4 ($p = 0.00$). A statistically significant difference was found for all scores between the two groups. The results obtained are summarized in Table 1.

Subgroup analysis was performed according to gender. In the healthy group, the total meiboscore was 2.8 ± 1.3 in women and 3.7 ± 1.7 in men. The difference was statistically significant ($p = 0.03$). There was no statistically significant difference in all other parameters between men and women in the healthy group ($p > 0.05$). In the blepharitis group, there was no statistically significant difference in the parameters according to gender ($p > 0.05$).

DISCUSSION

The primary goal of our study was to investigate the effects of chronic blepharitis on MG and eventually on the tear film layer in the geriatric patients. Additionally, we determined whether the upper or lower lid MG is more affected in patients with chronic blepharitis and healthy subjects in the geriatric patients. Furthermore, we observed the effects of tear film changes on the activities of daily living in the blepharitis and control groups through OSDI scoring.

Blepharitis is a chronic disease that significantly affects the ocular surface. Posterior blepharitis often results in significant eyelid margin abnormalities, such as telangiectasia, swelling, and hyperemia (2,14). Jester et al. (14) reported that these findings are associated with the keratinization abnormalities of the ductal epithelium that led to increased obstruction of the MG orifices and evaporation of tear film.

Meibography was first described in 1977 by Tapie using infrared light (15). Over the years, meibography has gained importance and has been used to evaluate MGD in the clinic. Non-contact meibography is often routinely used nowadays to demonstrate changes in the MG morphology. Meibography has two prominent scoring systems. The first of these was defined by Arita et al. (7,11) through their study where in the meiboscore was based on MG dropout. Conversely, Call et al. (16) suggested that other visible changes, such as MG dropout, gland distortion, and gland shortening, are crucial factors to be considered in meibography.

Table 1. The results of the study are summarized.

	Blepharitis group	Control group	*P
Total meiboscore	3.6 ± 1.7	3.0 ± 1.4	0.03
Non-invasive first TBUT	8.0 ± 4.8	10.4 ± 5.7	0.01
Non-invasive mean TBUT	9.7 ± 4.0	11.4 ± 5.0	0.03
Invasive TBUT	7.1 ± 3.0	8.6 ± 3.1	0.00
OSDI scores	27.4 ± 11.7	18.0 ± 6.4	0.00

TBUT: Tear break-up time, OSDI: Ocular surface disease index, *P = Independent samples t-test was used

Previous studies have shown that MGD increases with age (5,11). Moreover, the adverse effects of MGD in blepharitis are well known (2,3,5). However, to the best of our knowledge, no studies have been performed regarding the changes in MG in patients with chronic blepharitis and geriatric patients. Considering that DED is more common in the geriatric patients, we believe that this study is useful to better understand the underlying etiological factors. This effect can be understood well in the geriatric patients and can prove critical regarding preventive medicine use. Meticulous treatment of chronic blepharitis observed in these patients can significantly help with MGD and DED prophylaxis in the future.

The present study had few limitations. First, it was a retrospective study. Second, only a limited number of cases were found as per the study criteria. Third, only meibography and TBUT were used to evaluate MGD and the tear film layer, and the OSDI score was used to assess the effects of these on the activities of daily living.

The findings of the present study suggest that meiboscore values and TBUT durations are significantly reduced in geriatric patients with chronic blepharitis. In addition, these changes led to significant limitations in the activities of daily living of the patients. Aging, blepharitis, MGD, and DED were found to be correlated. Meibography and TBUT tests are thought to be useful tools in clinical practice. Moreover, meibography can be considered a beneficial diagnostic method to observe the changes in MG morphology.

Our study is concordant with the literature. A study by McCann et al. (3) found significantly lower tear and MG function in patients with blepharitis. Additionally, they found that the tear evaporation rate was markedly higher in the blepharitis group than the group of healthy individuals. Alsuhaibani et al. (17) explained that MG could range from mild to total dropout in patients with blepharitis. Finis et al. (18) and Arita et al. (11) showed that the total meiboscore increased significantly with age.

Lately, in vivo confocal microscopy (IVCM) has been used to demonstrate changes in MG. Randon et al. (19) showed that significant changes in MG could be found in patients with blepharitis using IVCM. One of the most significant findings of this study is the strong correlation between IVCM scores and meibography scores. Their study considered IVCM to be another valuable method that could demonstrate MGD.

Recently Arita et al. (20) showed that male sex was associated with MGD and female sex was associated with dry eye. On the other hand, Amano et al. (21) didn't find a significant relationship between sex with MGD in their study. Viso et al. (22) explained that the prevalence of asymptomatic

MGD is more common than symptomatic MGD. In this study, MGD was found to be higher in men in asymptomatic cases but there was no statistically significant a difference between two genders in symptomatic cases.

In our study, subgroup analyses showed that only meiboscore was higher in males among all parameters in healthy group, whereas there was no difference between women and men in blepharitis group.

We firmly believe that non-invasive meibography and TBUT tests are useful tools in the etiological evaluation of MGD and DED, which are common nowadays. Furthermore, non-invasive meibography can prove beneficial as a standard diagnostic method alongside other diagnostic tests to evaluate patients with MGD and DED. Nonetheless, further prospective randomized studies with more participants are required to validate the data of the present study.

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RESEARCH

COMPARISON OF INDICATIONS AND RESULTS OF PENETRATING KERATOPLASTY IN OLDER GERIATRIC PATIENTS WITH THOSE IN YOUNGER GERIATRIC PATIENTS

Abstract

Introduction: This study aimed to compare the indications and outcomes of penetrating keratoplasty in geriatric patients and to compare the younger geriatric patients with older geriatric patients.

Materials and Method: We evaluated the data of 489 eyes of 427 patients who underwent corneal transplantation surgery between August 2010 and July 2015 at a tertiary referral center in Turkey. We included 90 eyes of 81 patients aged ≥ 65 years with at least 1-year follow-up data were. The patients were divided into Groups 1 and 2 comprising patients aged 65–79 and ≥80 years, respectively.

Results: Groups 1 and 2 included 66 and 24 eyes, respectively. Bullous keratopathy was the most common indication for penetrating keratoplasty surgery in both groups (Group 1=34.9%, Group 2=66.7%, p=0.036). The incidence of secondary glaucoma after surgery (Group 1=18.2%, Group 2=15.6%, p=0.254) and graft survival period (Group 1=29.9±15.8 months, Group 2=26.7±13.2 months, p=0.374) were not significantly different between the two groups. The graft rejection and failure rates between the groups were analyzed, and no difference was observed between them (p=0.531, chi-squared=0.392 for graft rejection; p=0.699, chi-squared=0.150 for graft failure).

Conclusion: Bullous keratopathy as an indication for penetrating keratoplasty is significantly more common in older geriatric patients. The outcomes of penetrating keratoplasty in older geriatric patients are as good as those in younger geriatric patients.

Keywords: Corneal transplantation; Graft survival; Graft rejection; Turkey; Penetrating keratoplasty

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ARAŞTIRMA

İLERİ YAŞ VE DAHA GENÇ GERİATRİK HASTALARDAKİ PENETRAN KERATOPLASTİ ENDİKASYONLARININ VE SONUÇLARININ KARŞILAŞTIRILMASI

Öz

Amaç: Geriatrik hastalarda, penetran keratoplasti endikasyonları ve sonuçlarını değerlendirmek, daha genç geriatrik hastalar ile daha yaşlı geriatrik hastaları karşılaştırmaktır.

Gereç ve Yöntem: Türkiye'deki bir üçüncü basamak referans merkezinde Ağustos 2010 ile Temmuz 2015 yılları arasında penetran keratoplasti cerrahisi uygulanan 427 hastanın 489 gözünün verileri incelendi. 65 yaş ve üzerinde cerrahi uygulanan ve cerrahi sonrası en az 1 yıl takip edilen 81 hastanın 90 gözü çalışmaya alındı. Hastalar 65-79 yaş arası Grup 1, 80 yaş ve üzeri Grup 2 olmak üzere iki gruba ayrıldı.

Bulgular: Grup 1'de 66 göz Grup 2'de ise 24 göz mevcuttu. Her iki grupta da en sık penetran keratoplasti cerrahisi endikasyonu büllöz keratopatiydi. (Grup 1'de %34,9, Grup 2 'de %66,7 p=0,036). Cerrahi sonrası sekonder glokom gelişimi (Grup 1 %18,2,Grup 2 %15,6 p=0,254) ve greft sağkalımı (Grup 1 29,9 ± 15,8 ay,Grup 2 26,7 ± 13,2 ay, p=0,374) açısından iki grup arasında fark yoktu. Greft reddi ve yetmezliği açısından da her iki grup arasında istatistiksel fark saptanmadı. (Greft reddi için p=0,531 ki kare=0,392; greft yetmezliği için p=0,699 ki kare=0,150).

Sonuç: Daha yaşlı geriatrik hastalarda penetran keratoplasti endikasyonu olarak büllöz keratopati anlamlı bir şekilde daha yüksek oranda görülmektedir. Penetran keratoplasti cerrahisinin daha yaşlı geriatrik hastalardaki başarısı daha genç geriatrik hastalardaki kadar iyidir.

Anahtar sözcükler: Korneal transplantasyon; Doku reddi; Greft ömrü; Türkiye; Penetran keratoplasti

INTRODUCTION

The population of individuals aged >65 years is defined as elderly, and the proportion of the elderly population in Turkey was observed to be 8.3% in 2016 (1). When compared with the other age groups in the population, the fastest increase has been witnessed in elderly population aged >75 years (2). The ratio of people with visual disabilities in Turkey is 1.4%; of these, 15.8% are aged >65 years (3) and according to the 1998 data in Southeast Turkey, corneal blindness accounted for 15% of all causes of blindness (4).

Chronic diseases , sensitivity to anesthetic agents and perioperative morbidity are more frequent in the elderly population aged >75 years (5,6). Surgeons must perform a benefit-risk analysis before corneal transplantation to avoid unnecessary surgical procedures. Therefore, the graft survival period and frequency of complications and graft rejections should be known in elderly patients. Here, the outcomes in Turkish geriatric patients with corneal transplantation were investigated. Furthermore, we compared the results in older geriatric patients with those in younger geriatric patients.

MATERIALS AND METHOD

After obtaining the local ethics committee approval (2017/427) and written informed consent from all patients, the data of 489 eyes of 427 patients who underwent corneal transplantation between August 2010 and July 2015 at a tertiary referral center in Turkey were analyzed retrospectively. Of these, 90 eyes of 81 patients aged >65 years with at least 1-year follow-up data were included in the

Table 1. Preoperative systemic diseases of the patients.

	Group 1 n (%)	Group 2 n(%)	Total n(%)	p
Hypertension	41 (69%)	11 (50%)	52 (64%)	0.167
Diabetes mellitus	22 (37%)	2 (9%)	24 (29.6%)	0.018*
Coronary artery disease	10 (17%)	-	10 (12.3%)	-
Chronic renal failure	3 (5%)	-	3 (3.7%)	-
Benign prostatic hyperplasia	3 (5%)	-	3 (3.7%)	-
Chronic obstructive pulmonary disease	2 (3.4%)	1 (4.5%)	3 (3.7%)	0.256
Hypothyroidism	2 (3.4%)	-	2 (2.5%)	-
Hyperlipidemia	2 (3.4%)	-	2 (2.5%)	-
Hepatitis C	2 (3.4%)	-	2 (2.5%)	-
Heart rhythm disorders	-	2 (9%)	2 (2.5%)	-
Osteoporosis	-	2 (9%)	2 (2.5%)	-
Asthma	1 (1.7%)	-	1 (1.2%)	-
Rheumatoid arthritis	1 (1.7%)	-	1 (1.2%)	-

*Significantly different

study. The patients were separated into Groups 1 and 2 comprising patients aged 65–79 and ≥80 years, respectively.

All surgeries were performed using a standard technique, and the donor corneal tissues were provided by the eye bank at the tertiary referral center. Donor–recipient age matching was not conducted. All surgeries were penetrating keratoplasties performed under general anesthesia. Donor buttons were cut 0.25-mm or 0.50-mm larger than the recipient bed using Barron radial vacuum trephines and Barron punches. The

Table 2. Indications for corneal transplantation surgery in the geriatric patients.

	Group 1 n(%)	Group 2 n(%)	p
BULLOUS KERATOPATHY	27 (40.9%)	16 (66.7%)	0.036*
Pseudophakic bullous keratopathy	23	15	
Aphakic bullous keratopathy	4	1	
PREVIOUS GRAFT FAILURE	18 (27.3%)	3 (12.5%)	0.167
Pseudophakic bullous keratopathy	5	1	
Corneal scar due to herpetic keratitis due to ocular trauma	5 4 1	- - -	
Keratoconus	4	-	
Corneal dystrophy Fuchs endothelial dystrophy Granular dystrophy Lattice corneal dystrophy	4 1 2 1	2 1 - 1	
CORNEAL SCAR	12 (18.2%)	3 (12.5%)	0.522
due to herpetic keratitis	9	-	
due to ocular trauma	1	-	
due to nonherpetic keratitis	2	3	
CORNEAL DYSTROPHY	6 (9.1%)	1 (4.2%)	0.441
Fuchs endothelial dystrophy	5	-	
Posterior polymorphous dystrophy	1	1	
CORNEAL DEGENERATION	2 (3.03%)	-	-
CORNEAL ECTASIA	1 (1.5%)	1 (4.2%)	0.450
Pellucid marginal degeneration	1	-	
Keratoconus	-	1	-
TOTAL	66 (100%)	24 (100%)	

*Significantly different

Figure 1. Evaluation of graft rejection in the geriatric patients who underwent penetrating keratoplasty with a Kaplan–Meier survival analysis (p=0.531, chi-squared=0.392).

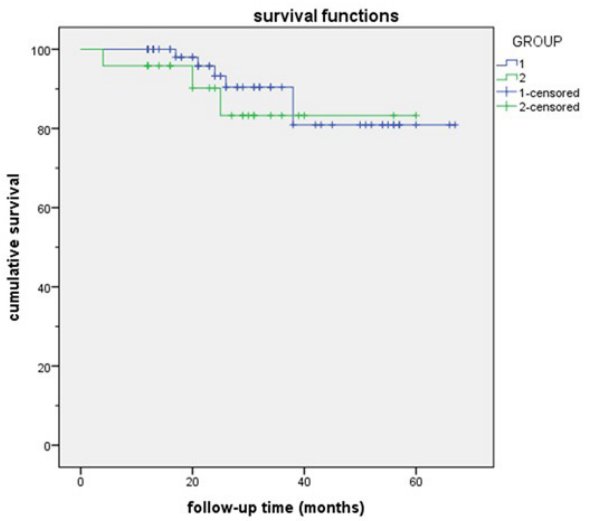
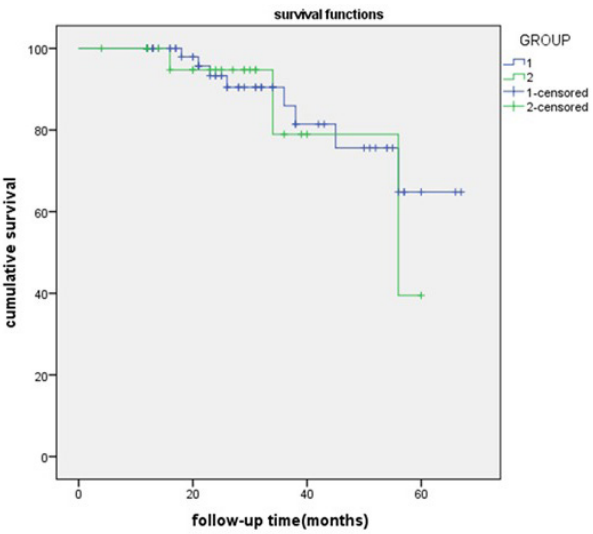


Figure 2. Evaluation of graft failure in the geriatric patients who underwent penetrating keratoplasty with a Kaplan–Meier survival analysis (p=0.699, chi-squared=0.150).



donor tissues were attached to the host tissue with interrupted or running 10-0 nylon sutures or a combination of both.

Postoperatively, 0.3% tobramycin was used four times daily for 10 days, and 1% prednisolone sodium phosphate was initiated 6–8 times daily and tapered off over 10–15 months. The sutures were removed when the sutures loosened or vascularization of the host cornea occured. The routine suture removal was performed between 12 and 30 months after the surgery. At each visit, the graft clarity was assessed by biomicroscopic examination, and the visual acuity was measured. The intraocular pressure was measured using an applanation tonometer. The irreversible loss of clarity of the graft for a minimum of 3 sequential months was defined as graft failure (7). Development of subepithelial infiltrates, keratic precipitates, endothelial rejection line, an anterior chamber reaction, or a corneal edema in a previously clear graft was defined as graft rejection (8). In the event of allograft rejection, 1% prednisolone sodium phosphate was initiated every hour.

The chi-squared test was used to compare the nominal data, and the Kaplan–Meier survival analysis test was used to compare graft survival and rejection among the groups. An independent t-test was used to compare the follow-up period between the groups, Pearson correlation analysis was used to evaluate the correlations between data in both groups, and The Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the statistical tests, with a p value <0.05 considered to be significant.

RESULTS

Geriatric patients accounted for 18.4% of all patients undergoing corneal transplantation between August 2010 and July 2015. Groups 1 and 2 comprised 66 (73%) and 24 (27%) eyes, respectively. The mean age of the patients undergoing surgery was 70.4±3.5 and 81.5±2

Table 3. The corneal transplantation outcomes and graft survival rates of the geriatric patients.

	Group 1	Group 2	Total	p value
Mean BCVA before surgery (logMAR)	1.6±0.51	1.85±0.4	1.67±0.5	0.040*
Final mean BCVA after surgery (logMAR)	1.06±0.67	1.07±0.63	1.06±0.66	0.938
Highest mean BCVA after surgery (logMAR)	0.7±0.5	0.82±0.54	0.73±0.5	0.324
Graft rejection	6/66 (9.1%)	3/24 (12.5%)	9/90 (10%)	0.634
Graft failure	8/66 (12.1%)	3/24 (12.5%)	11/90 (12.2%)	0.961
Secondary glaucoma after surgery	12/66 (18.2%)	2/24 (8.3%)	14/90 (15.6%)	0.254
Cataract after surgery	3/66 (4.5%)	0/66 (0%)	3/90 (3.3%)	-
Keratitis after surgery	3/66 (4.5%)	0/66 (0%)	3/90 (3.3%)	-
Retinal detachment after surgery	1/66 (1.5%)	0/66 (0%)	1/90 (1.1%)	-
1-year graft survival rates	100%	100%		
2-year graft survival rates	93.3±0.037%	94.7±0.051%		
3-year graft survival rates	85.9±0.062%	78.9±0.150%		
5-year graft survival rates	64.8±0.125%	39.5±0.289%		
Mean graft survival rate during the mean follow-up period	90.5±0.046%	94.7±0.051%		

*Significantly different, BCVA: best corrected visual acuity.

years and the mean follow-up period was 31.65±16.66 and 28.25±13.17 months in Groups 1 and 2, respectively. No significant difference was observed between the study groups with regard to the sex (p=0.567) or the follow-up period (p=0.514).

The preoperative systemic diseases of the patients are shown in Table 1. In Groups 1 and 2, 22 (37.3%) and 2 (9.1%) patients had three or more systemic diseases, respectively; however, the difference was not statistically significant (p=0.254).

The indications for corneal transplantation in the geriatric patients are listed in Table 2. Bullous keratopathy was the most common indication for transplantation surgery in both groups and was diagnosed significantly more often in Group 2 than in Group 1 (p=0.036).

No significant difference was observed between the two groups with regard to the coexisting ocular findings before corneal transplantation, which were cataract (Group 1: 34.9%; Group 2: 20.8%), glaucoma (Group 1: 38%; Group 2: 20.8%), blepharitis (Group 1: 27.3%; Group 2: 29.2%), dry eyes (Group 1: 19.7%; Group 2: 16.7%), and retinopathy (Group 1: 9.1%; Group 2: 4.2%). Posterior chamber intraocular lenses (PCIOLs) were observed in 62.1% and 79.2% of eyes in Groups 1 and 2, respectively, and were the most

common finding in both groups.

Nineteen cases (28.8%) in Group 1 and 8 cases (33.3%) in Group 2 underwent surgeries combined with corneal transplantation (p=0.677); however, no significant difference was observed between both groups. Phacoemulsification and PCIOL implantation were observed in 9 eyes in Group 1 and 2 eyes in Group 2 and were the most common surgeries combined with the corneal transplantation.

Ten eyes (15.2%) in Group 1 and three eyes (12.5%) in Group 2 underwent additional postoperative surgeries, with no statistically significant difference between the two groups (p=0.752).

The outcomes of corneal transplantation in the geriatric patients are shown in Table 3. No significant difference was observed between the groups with regard to graft rejection using the Kaplan–Meier survival analysis test (p=0.531, chi-squared=0.392) (Figure 1). In this study, the overall average graft survival period was 29.1±15.2 months, whereas it was 29.9±15.8 months in Group 1 and 26.7±13.2 months in Group 2. No statistically significant difference was noted between the two groups (independent t-test, p=0.374). The graft survival rates for each year are shown in Table 3.

Similarly, no difference was detected between the study groups with regard to the graft failure rate using the Kaplan–Meier survival analysis (p=0.699, chi-squared=0.150) (Figure 2). In addition, the patients who underwent surgery for bullous keratopathy were evaluated. No differences were observed in terms of the graft rejection (p=0.516, chi-squared=0.422) and failure (p=0.702, chi-squared=0.146) between the two groups using the Kaplan–Meier survival analysis test.

DISCUSSION

In this study, all the performed corneal transplantation surgeries were penetrating keratoplasties. Partial thickness surgeries have been increasing worldwide. Although endothelial keratoplasty is the most common technique preferred in geriatric patients in developed countries (9), penetrating keratoplasty was the only technique selected for these geriatric patients because of the absence of precut tissue facilities for descemet stripping automated endothelial keratoplasty .

Endothelial disorders were the main cause and most common indication of corneal transplantations in the geriatric patients in our study, which is consistent with the literature (10-12); moreover, they were diagnosed significantly more often in Group 2 (p=0.036). Previous graft failure was the second most common indication, and corneal ectasia was the least common indication in both groups.

Recently, advances in the surgical techniques for cataract surgery have improved the rate of endothelial cell loss and enhanced the optical outcomes of patients (13). This justifies the lesser number of bullous keratopathy cases in Group 1 than in Group 2.

In the study by Duman et al., Fuchs' endothelial dystrophy (41%) was the leading indication, and pseudophakic bullous keratopathy (26%) was the second most frequent indication for corneal transplantation in geriatric patients (11). However, Fuchs' endothelial dystrophy was diagnosed only in Group 1 (7.6%) in our study. This difference can be explained by the genetic differences between the two study populations. Western regions such as the United States, Canada, and Europe have reported more Fuchs' endothelial dystrophy cases than the Middle East, Asia, Oceania, and South America (14).

Corneal transplantation considerably improved postoperative vision in both groups, with no statistically significant difference between them. The highest mean BCVA after surgery was 0.7±0.5 logMAR in Group 1 and 0.82±0.54 logMAR in Group 2 (p=0.324).

No significant difference was observed between the groups with regard to secondary glaucoma (p=0.123); however, 12 eyes (18.2%) in Group 1 and 2 eyes (8.3%) in Group 2 had secondary glaucoma. Karadag et al. reported that the prevalence of glaucoma after penetrating keratoplasty was 16.6% in a study regarding the Turkish population, which is consistent with our study (15). However, Duman et al. reported that glaucoma following corneal transplantation was more frequent in patients aged >80 years than in those aged 65–80 years (11). No significant difference was observed between the groups with regard to graft rejection (p=0.531, chi-squared=0.392) and failure (p=0.699, chi-squared=0.150) (Figures 1 and 2). In addition, No difference was observed between the two subgroups that underwent surgery for bullous keratopathy diagnosis with regard to graft rejection (p=0.516, chi-squared=0.422) and failure (p=0.702, chi-squared=0.146).

In the current study, the overall average graft survival period was 29.1±15.2 months; it was 29.9±15.8 months in Group 1 and 26.7±13.2 months in Group 2, with no significant difference between them (p=0.374, independent t-test). The graft survival rate of the corneal transplantations at 1 year was 100% in both groups. The 2-, 3-, and 5-year graft survival rates were 93.3%, 85.9%, and 64.8% in Group 1 and 94.7%, 78.9%, and 39.5% in Group 2, respectively. The 1-year survival rates of penetrating keratoplasty in the literature were 80%–93.5%; however, these were dependent on the indication for the transplantation (16, 17). The 5-year survival probability of the penetrating keratoplasty in the literature is 83.0%; it is more favorable in ectasia cases (96.0%) and least favorable in pseudophakic corneal edema (67.0%) and regraft (64.0%) cases (8).

An older recipient age has been investigated in terms of the graft failure and rejection in previous studies, and different results have been reported. Williams et al. and Inoue et al. suggested that the relative risks of graft failure in recipients aged >50 years were 3.03 and 2.38, respectively (18, 19). In the Singapore Corneal Transplant Study (20), a poorer prognosis was reported in older patients, which was similar to that in the study by Williams et al. However, in the cornea-donor study (21), the patient's age was not associated with the risk of graft failure, whereas Vail et al. reported that the risk of graft rejection was decreased with increasing recipient age (22).

Duman et al. compared recipients aged 65–80 years with those aged >80 years (11); no significant difference was observed in terms of the graft survival and rejection rates. The recipient age was evaluated in another study (10), which reported that the corneal graft survival decreases significantly in recipients aged ≥60 years. However, the difference in the survival between the groups aged 60–79 and >80 years was not significant.

In terms of the total number of additional postoperative surgeries, no significant difference was observed between the groups (p=0.752). Among all 90 eyes, 3 (3.3%) had cataracts and 1 (1.1%) had retinal detachment, with no incidence of endophthalmitis after corneal transplantation. In the literature, the incidence of infectious keratitis following penetrating keratoplasty in high-income countries was 1.76%–4.9% (23), whereas 3 eyes (3.3%) with keratitis were observed in our study.

This study has some limitations; for example, the data was retrospective, and the number of cases was small. In addition, patients with three or more preoperative systemic diseases (37.3% vs. 9.1%, p=0.254), and those preoperative glaucoma was more frequent in Group 1 (38% vs. 20.8%, p=0.129) than in Group 2, although the difference was statistically insignificant. Moreover, the indication of previous graft failure in Group 1 was higher than that in Group 2 (27.3% vs. 12.5%, p=0.167). However, the difference was statistically insignificant.

Both preoperative glaucoma and a repeat penetrating corneal transplantation are risk factors for graft failure (21, 24). When the surgeons

were planning corneal transplantation in patients in Group 2, they may have selected those with less systemic diseases and without glaucoma or previous corneal transplantation. In addition, the patients with three or more systemic diseases may not be able to visit the corneal clinics because of their impaired health. Therefore, this may have resulted in a bias regarding the patient selection criteria.

In conclusion, this study revealed that penetrating keratoplasty improves the postoperative vision in geriatric patients, with no significant difference between younger geriatric patients and older geriatric patients in terms of the graft survival and postoperative complications. However, further prospective studies with larger samples may yield better results.

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RESEARCH

HELICOBACTER PYLORI INFECTION IS AN AVOIDABLE RISK FACTOR FOR PARKINSON'S DISEASE

Abstract

Introduction: : Gram-negative bacteria such as Helicobacter pylori (HP) are becoming increasingly implicated in the etiology of Parkinson's disease (PD). This study aimed to investigate the association between PD and HP infections.

Materials and Method: Eighty-three patients with PD and age- and sex-matched healthy control subjects with no history of PD were enrolled. Patients with secondary Parkinsonism and severe cognitive impairment were excluded. All patients were staged according to the Hoehn and Yahr scale. We obtained 10 mL venous blood samples from all patients and controls. The plasma was separated, and samples were stored at −200°C. IgG antibodies developing against HP were investigated using the ELISA method. Values >5 IU/ml were considered positive.

Results: Eighty-three patients and 81 controls were included in the study. HP IgG was positive in 87% of the patient group and in 74% of the control group. The median antibody titer in the patient group was higher than that in the control group (p=0.0019). No significant relation was observed between disease severity and IgG positivity (p=0.947). However, a moderate correlation was observed between disease severity and mean IgG level (r=0.277, p=0.011). HP IgG positivity (OR 3.15, 95% CI 1.23–8.07, p=0.002), a family history of PD (OR 2.57, 95% CI 1.02–4.13, p= 0.03), and male gender (OR 2.05, 95% CI 0.95–6.99, p= 0.02) increase the likelihood of PD.

Conclusion: HP infections may trigger various abnormal or enhanced immunological processes in patients diagnosed with PD; these abnormal immunological activities are probably involved in the disease pathogenesis.

Keywords: Parkinson disease, Helicobacter pylori, Disease severity

ARAŞTIRMA

PARKİNSON HASTALIĞI İÇİN ÖNLENEBİLİR BİR RİSK FAKTÖRÜ OLARAK HELİCOBACTER PYLORİ ENFEKSİYONU

Öz

Giriş: Helicobacter pylori (HP) gibi Gram-negatif bakteriler Parkinson Hastalığı'nda (PH) etiyolojik etmen olabilir. Bu çalışmada PH ve HP enfeksiyonu arasındaki ilişki araştırıldı.

Gereç ve Yöntem: Parkinson Hastalığı tanısı olan 83 hasta ve yaş-cinsiyet uyumlu olan sağlıklı kontrol grubu çalışmaya alındı. Sekonder parkinsonizm tanısı olan ve ağır bilişsel etkilenmesi olan hastalar çalışma dışı bırakıldı. Tüm hastalar Hoehn Yahr skalasına göre klinik olarak evrelendirildi. Çalışma grubundan 10 ml venöz kan örnekleri toplandı ve plasma ve serumları ayrılarak, örnekler -200°C\'de muhafaza adildi. HP'ye karşı oluşan IgG'ler ELİSA yöntemiyle bakıldı ve değerin >5 IU/ml\'in üzerinde olması pozitif olarak değerlendirildi.

Bulgular: Çalışmaya 83 hasta grubu ve 81 sağlıklı kontrol grubu dahil edildi. Parkinson hastalığı olan grupta %87, kontrol grubunda %74 oranında HP IgG pozitifliği saptandı. Hasta grubunun ortalama antikor titresi kontrol grubuna göre anlamlı olarak daha yüksekti (p=0.0019). Hastalık şiddeti ve IG pozitifliği arasında korelasyon saptanmadı (p=0.947). Ancak, hastalık şiddeti ile ortalama IgG düzeyleri arasında orta derecede korelasyon saptandı r=0,277, p=0.011). HP IgG pozitifliğinin (OR 3.15, 95% CI 1.23–8.07, p=0.002), ailede PH öyküsü olmasının (OR 2.57, 95% CI 1.02–4.13, p= 0.03) ve erkek cinsiyetin (OR 2.05, 95% CI 0.95–6.99, p= 0.02), PH olma olasılığını anlamlı biçimde artırmış olduğu saptandı.

Sonuç: : HP enfeksiyonu, çeşitli immünolojik yolaklar üzerinden PH 'yı tetikleyebilir ve bu anormal immün reaksiyonlar hastalık patogenezinde olasılıkla rol oynamaktadır.

Anahtar sözcükler: Parkinson hastalığı; Helicobacter pylori; Hastalık şiddeti

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide (1). It was first described by James Parkinson in 1817, although the etiology has remained unclear for the following 200 years. Genetic and numerous environmental factors are involved in the development of the condition, as with similar neurodegenerative diseases (2). Recent research has suggested that infections may be involved in the etiology of PD (3-6). Cytomegalovirus, Epstein Barr virus, Herpes Simplex Type I, Borrellia burgdorferi, Chlamydia pneumoniae, and Helicobacter pylori (HP) are some of the main causative agents (7). HP infections are widespread, infecting as much as 50% of the world population. Factors such as prevalence of HP infections increase with age. Lower socioeconomic status, contact with contaminated water, and living in overcrowded environments increase the prevalence of infections and reduce the age of infection by this agent (1). HP is a gram-negative bacterium that settles in the gastric epithelium. Due to urease production, it is resistant to gastric acid and can thus lead to chronic inflammation. Although it is commonly acquired during childhood, HP can result in chronic infections. Although it causes no clinical problems, it may nevertheless contribute to various gastrointestinal and extra-gastrointestinal diseases (8-11). The aim of this study was to investigate the potential association between PD and HP.

MATERIALS AND METHOD

The research was designed as a multicenter cohort study. All patients and all healthy control subjects provided verbal informed consent to participate in the study. Approval for the research project was granted by the Samsun Training and Research Hospital ethical committee.

1.1.Participants

Eighty-three patients meeting the UK Parkinson's Disease Society's brain bank diagnostic criteria were included in the study. Eighty-one healthy control subjects were matched with the patients in terms of age and sex. We excluded patients with secondary Parkinsonism or severe cognitive impairment, subjects treated with antibiotics for HP within the previous year, and individuals with a history of inflammatory or neoplastic diseases. All patients underwent Hoehn and Yahr scale disease staging. The research was approved by the local ethical committee. Informed written consent was obtained from all patients and healthy controls.

1.2. Procedures

We obtained 10 mL venous blood samples from all members of the patient and control groups. The plasma was separated, and samples were stored at −200°C. IgG antibodies against HP were investigated using the ELISA method (DiaPro, Italy). Values ≥5 IU/ml were considered positive.

2. Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 16.0 for Windows was used for all statistical analyses, and p values <0.05 were considered statistically significant for all results. The chi-square test was used to compare categorical variables, and p values were calculated using Fisher's test where necessary. For data with non-normal distributions, the mean values for two independent groups were compared using the nonparametric Mann–Whitney U-test. Pearson correlation analysis was used to determine the direction and level of correlation between variables, and variables considered to affect one another were subjected to multiple regression analyses. The association between the odds of PD and HP IgG positivity was assessed using a mutually-adjusted multivariate logistic regression model, controlling for potential confounders and providing an odds ratio (OR) and corresponding 95% confidence interval (95%CI).

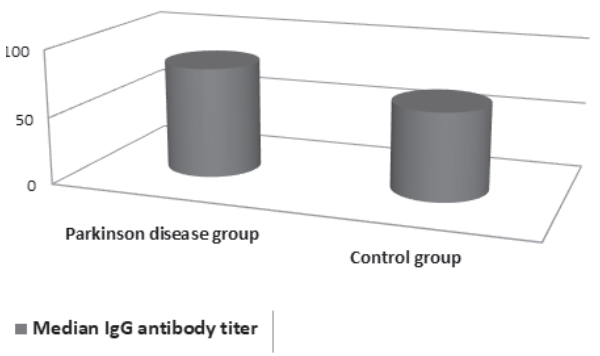
RESULTS

Eighty-three patients (F/M, 34/49) and 81 controls

(F/M, 45/36) were included in this study. The mean age of the patient group was 68.73±8.6 (45–86) years, and the mean age of the control group was 69.26±8.42 (50–87) years. The difference in age between the patient and control groups was not statistically significant (p>0.05). HP IgG was positive in 73 subjects (87%) in the patient group and in 60 (74%) in the control group. This difference between the two groups was statistically significant (p=0.028). The median antibody titer in the patient group was higher than that in the control group. The difference between the patient and control groups was significant (82.17±92.15 IU/ml and 64.84±88.99 IU/ml, respectively) (p=0.019) (Figure 1).

Mean duration of disease in the patient group was 7.7±6.22 (1–30) years. No correlation was determined between duration of disease and mean IgG (r=0.137). The patient group was examined in terms of IgG positivity, based on tremor or bradykinesia onset characteristics. Bradykinesia predominated at onset in 36 of the 73 patients who were positive for HP IgG antibody, while tremor predominated in 37. Onset involved tremor in six of the 10 IgG antibody negative patients, while onset predominantly involved bradykinesia in four. No statistically significant difference was determined between the two groups (p=0.29).

Figure 1. Median IgG titer of both groups.



Familial PD was observed in 15 members of the patient group, but was not present in 68 patients. HP IgG positivity was present in 14 of the 15 patients with familial PD, and IgG positivity was present in 59 of the 68 patients without familial PD. The difference was not statistically significant (p=0.42). HP positive IgG values according to the Hoehn–Yahr scale are presented in Table 1. No significant relationship was observed between disease severity (as indicated by Hoehn–Yahr score) and IgG positivity (p=0.947). However, a moderate correlation was observed between disease severity and mean IgG level (r=0.277, p=0.011). When a mutually-adjusted multivariate logistic regression model was constructed for both groups, HP IgG positivity was determined to increase the likelihood of PD (OR 3.15, 95% CI 1.23–8.07, p=0.002). Additionally, factors such as a family history of PD (OR 2.57, 95%CI 1.02–4.13, p= 0.03) and male sex (OR 2.05, 95%CI 0.95–6.99, p= 0.02) also increased the likelihood of PD.

DISCUSSION

Although the relationship between HP and PD has not yet been completely elucidated, the commonly accepted thesis is that HP has no direct impact on the disease. However, an immune response due to chronic inflammation caused by HP affects the central nervous system, particularly dopaminergic receptors located in the substantia nigra (12-16). Chen et al. observed that injection of IgG obtained from the sera of patients with PD into the substantia nigra in rats resulted in the destruction of cells producing tyrosine hydroxylase (15). In addition, endotoxins of gram-negative bacteria, including HP, may increase the production of inflammatory cytokines, such as TNFα, and stimulable nitric oxide synthase in cultured microglia and astrocytes (13). Inflammatory cytokines, such as ILβ, TNFα, and INF-Ɣ, and nitric oxide, derived from microglia and non-neuronal cells may lead to the degeneration of dopaminergic neurons (17-18).

Table 1. IgG positivity rates according to the Hoehn-Yahr scale.

	HP IgG positive above 5		Total
	Negative (%)	Negative (%)	
Only unilateral involvement, usually with minimal or no functional disability (1)	1 (10.0%)	10 (13.7%)	11 (13.3%)
Bilateral or midline involvement without impairment of balance (2)	3 (30.0%)	16 (21.9%)	19 (22.9%)
Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent (3)	4 (40.0%)	24 (32.9%)	28 (33.7%)
Severely disabling disease; still able to walk or stand unassisted (4)	2 (20.0%)	21 (28.8%)	23 (27.7%)
Dependent on bed or wheelchair unless aided (5)	0 (0.0%)	2 (2.7%)	2 (2.4%)
Total	10 (100.0%)	73 (100.0%)	83 (100.0%)

The blood and/or cerebrospinal fluid of PD patients has been observed to contain antibodies against sympathetic and dopaminergic neurons. Systemic inflammation occurring because of the development of antibodies may accelerate neurodegeneration, and treating infections may help improve patients' clinical conditions (12-20). Chronic HP infections can disrupt the blood–brain barrier and result in microglial activation, and increase the incidences of neuronal destruction and mortality (16). In the light of this information, we examined the relationship between the presence of HP antibodies and IgG titer and PD. The level of HP IgG antibodies was higher in the patient group than in the healthy control group. The mean IgG titer was significantly higher among patients with PD. Previous studies have reported lower rates of HP positivity, whereas the values obtained in our study were considerably higher (5,21). We also determined higher levels of HP antibody elevation in our control group. The variation among studies in terms of HP IgG antibody positivity may be attributed to factors that may vary between countries, including lifestyle differences, eating habits, and genetic disposition. One meta-analysis published in 2017 reported an OR of 1.59 for patients with PD and HP. Subgroup analysis revealed a higher OR in Asia than in Europe (1.99 and 1.55, respectively) (22). In another meta-analysis, HP infection was identified as a risk factor in terms of PD, and a decrease in UPDRS scores, indicating severity of PD, was achieved with HP eradication (23). In our study, when all potential confounding factors were added together, HP increased the risk of PD 3.15-fold. The risk also increased in males, and among subjects with a family member with PD.

HP infection has long been known to cause gastrointestinal diseases such as chronic gastritis and peptic ulcer. However, studies in recent years have also shown that it may also predispose to neurological diseases such as cerebrovascular disease, multiple sclerosis, and Alzheimer's (24,25,26). The eradication of HP infection, also regarded as a societal problem, may be beneficial

Table 2. Impact of some factors in parkinson's disease

	Odds Ratio (OR)	P
HP IgG positive	3.15	0.017
Age	1.01	0.644
Male gender	2.05	0.043
Family history of PD	2.57	0.04
Total	835	100.0

in reducing the development of severity of neurological disease that frequently also entails socioeconomic burdens.

HP infections may trigger various abnormal or enhanced immunological processes in patients diagnosed with PD, and these abnormal immunological activities are probably involved in the pathogenesis of the disease. This association has been described as significant in previous studies. However, two questions remain unanswered. The first concerns the identity of the underlying pathophysiological mechanism. Secondly, it is unclear whether infection accelerates the disease process or initiates it. If this association is scientifically proven among patients with HP, antibiotic treatment may reduce the prevalence of PD or decelerate the progression of existing PD.

CONCLUSION

This study investigated the association between the presence of IgG as a serological indicator of HP infection and PD. However, the processes underlying this association were not investigated and our findings suggest a significant association. However, we were unable to conclude that HP infection represents a risk factor for PD. Further, more detailed studies with longer follow-up periods in which the processes involved in PD, HP infection, and immunological changes are closely monitored are required to confirm this association.

CONFLICTS OF INTEREST:

None.

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RESEARCH

STRABISMUS IN GERIATRIC PATIENTS: ETIOLOGY AND CLINICAL FEATURES

Abstract

Introduction: As life expectancy is continuously increasing, health issues, such as strabismus that has a functional and psychosocial impact on the quality of life, have gained more importance and require a solution. In the present study, we aimed to describe and determine the strabismus etiology and clinical features in patients aged ≥65 years who were examined in a strabismus clinic.

Materials and Method: We retrospectively examined the data of patients aged ≥65 years who were admitted to the strabismus clinic between July 2018 and July 2019. The findings of the ophthalmological and orthoptic examination as well as the strabismus etiology, intervention required, and chief complaints were all recorded.

Results: We extracted the medical records of 40 patients (16 female and 24 male) aged ≥65 years who were examined in the strabismus clinic. The chief complaint was diplopia in 30 (75%) patients, followed by ocular deviation in 10 (25%) patients. The deviation was horizontal in 26 (65%) patients. The most common etiology was thyroid eye disease (6 patients; 15%), followed by diabetes (5 patients, 12.5%), hypertension (5 patients, 12.5%), trauma (3 patients, 7.5%), cerebrovascular event (3 patients, 7.5%), intracranial mass (3 patients, 7.5%), and secondary deviation (3 patients, 7.5%). Moreover, 11 (27.5%) patients underwent surgery, whereas 17 (42.5%) patients received nonsurgical treatment; 14 (35%) patients did not re-visit the strabismus clinic.

Conclusion: Strabismus can be seen in elderly individuals. The underlying etiology, such as trauma and cerebrovascular events, may be life threatening and requires prompt diagnosis and treatment.

Keywords: Cranial nerve palsy; Diplopia; Geriatric; Ocular misalignment; Strabismus; Surgery

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ARAŞTIRMA

GERİATRİK HASTALARDA ŞAŞILIK: ETİYOLOJİ VE KLİNİK ÖZELLİKLER

Öz

Giriş: Yaşam beklentisinin devamlı bir şekilde uzaması ile fonksiyonel ve psikososyal etkisi olan şaşılık gibi sağlık sorunları daha fazla önem kazanmakta ve bir çözüm gerektirmektedir. Bu çalışmada, şaşılık kliniğinde görülen 65 yaş ve üstü hastalarda şaşılık etiyolojisini ve klinik özelllikleri belirlemeyi ve tanımlamayı amaçladık.

Gereç ve Yöntem: Şaşılık kliniğine Temmuz 2018-Temmuz 2019 tarihleri arasında başvuran 65 yaş ve üstü hastaların verilerini retrospektif olarak inceledik. Oftalmolojik ve ortoptik muayene bulguları ve ayrıca şaşılık etiyolojisi, esas başvurma şikayetleri ve gerekli girişimler kaydedildi.

Bulgular: Şaşılık kliniğinde görülen altmış beş yaş ve üstü 40 hastanın (16 kadın, 24 erkek) tıbbi kayıtları çıkartıldı. Esas başvuru şikayeti 30 hastada (%75) çift görme idi ve bunu 10 hastada gözde kayma (%25) izliyordu. Kayma 26 hastada (%65) horizontal idi. En sık etiyoloji 6 hastada (%15) tiroid göz hastalığı iken bunu diyabet (5 hasta, %12,5), hipertansiyon (5 hasta, %12,5), travma (3 hasta, %7,5), serebrovasküler olay (3 hasta, %7,5), intrakranyal kitle (3 hasta, %7,5) ve sekonder kayma (3 hasta, %7,5) izliyordu. Onbir (%27,5) hasta ameliyat olurken 17 hastaya (%42,5) cerrahi dışı tedavi uygulandı. On dört hasta (%35) şaşılık kliniğine tekrar kontrole gelmedi.

Sonuç: Şaşılık yaşlı kişilerde de görülebilir. Altta yatan travma ve serebrovasküler olay gibi etiyolojiler hayatı tehdit edebilir ve hızlı tanı ve tedavi gerektirebilir.

Anahtar sözcükler: Cerrahi; Diplopi; Geriatrik; Kranyal sinir felci; Oküler hizalanmanın bozulması; Şaşılık

INTRODUCTION

Some of the eye diseases, such as cataract and macular degeneration, are related to the age of the individual. However, strabismus, defined as an ocular misalignment, can be observed in every age group, although it is typically encountered and diagnosed during childhood. Indeed, the incidence of strabismus increases with age and tends to be more frequent, particularly in those aged ≥60 years (1,2). In adults, this disease is either associated with childhood-onset strabismus or newly developed due to trauma, ocular/nonocular surgery, or neurological disease (2). The ocular deviation can be horizontal, vertical, torsional, or combined as well as be paralytic or nonparalytic. The third, fourth, and sixth cranial nerve palsy results in the paralysis of the extraocular muscles and may occur due to older age, diabetes mellitus, hypertension, or hyperlipidemia, which are all factors that cumulatively result in atherosclerotic changes (3, 4).

In the present study, we aimed to describe the clinical features of strabismus in patients aged ≥65 years who were examined in a strabismus clinic for the past 1 year and to determine the underlying causes and management of strabismus.

MATERIALS AND METHOD

A retrospective review of the records between July 2018 and July 2019 of the strabismus clinic at Hacettepe University, Faculty of Medicine was conducted. The study was conducted in complete accordance with the tenets of the Declaration of Helsinki and was performed upon the approval of the Institutional Review Board. Data regarding patients aged ≥65 years were extracted and included the demographic characteristics, such as age and sex, and ophthalmological and orthoptic examination findings as well as information regarding the systemic comorbidities diagnosed and the surgical and nonsurgical interventions (prismatic glasses and botulinum toxin injection) employed for the management of strabismus.

Furthermore, the chief complaint at initial presentation, best corrected visual acuity, type of ocular deviation, amount of deviation in the primary position in prism diopters (PD), and underlying etiology, if identified, were noted. Alternate prism cover test was performed at near (1/3 m) and distance (6 m) fixation for measuring ocular deviation. Krimsky test was used when the visual acuity of the patient is insufficient for target fixation.

All statistical analyses were performed using IBM SPSS Statistics 23.0 software. Descriptive statistics were expressed as mean ± standard deviation or median (min-max) for quantitative data, according to the assumption of normal distribution, and as frequency for qualitative data. Chi-squared test was used for comparison. A $p < 0.05$ was accepted as statistically significant.

RESULTS

The data of 40 patients (16 female and 24 male) aged ≥65 years who were admitted to the strabismus clinic were included in the study. Mean patient age was 70.07 ± 6.16 (65-83) years.

Demographic and clinical characteristics of the patients are presented in Table 1. The mean best corrected visual acuity was 0.80 ± 0.20 in the right eye and 0.73 ± 0.26 in the left eye.

The chief complaint was diplopia with a frequency of 75% (30 patients) followed by ocular misalignment in 25% (10 patients). The onset of the complaint occurred during the past 1 month in 7 patients (17.5%). A horizontal deviation, occurring in 26 (65%) patients, was the most common type of ocular deviation in the primary position at initial presentation.

Mean ocular deviation was 16.8 ± 18.4 PD for near horizontal, 17.92 ± 18.99 PD for distance horizontal, 5.70 ± 11.42 PD for near vertical, and 5.65 ± 11.11 PD for distance vertical.

Table 1. Demographic and clinical characteristics of the patients aged ≥65 years at the initial presentation to the strabismus clinic

Demographic characteristics	No. of patients (%)
Sex	
Male	24 (60)
Female	16 (40)
Comorbidity	
Hypertension	15 (37.5)
Thyroid disease	9 (22.5)
Diabetes mellitus	7 (17.5)
Coronary heart disease	4 (10)
Chronic obstructive lung disease	2 (5)
Depression	2 (5)
Acne rosacea	1 (2.5)
Breast cancer	1 (2.5)
Intracranial aneurysm	1 (2.5)
Disease characteristics	
Laterality	
Unilateral	27 (67.5)
Bilateral	13 (32.5)
Chief complaint	
Diplopia	30 (75)
Ocular misalignment	10 (25)
Onset of the complaint	
≤1 month	7 (17.5)
2–11 months	6 (15)
≥1 year	27 (67.5)
Type of initial ocular deviation	
Horizontal	26 (65)
Vertical	5 (12.5)
Combined	9 (22.5)
Underlying etiology	
Thyroid eye disease	6 (15)
Diabetes mellitus	5 (12.5)
Hypertension	5 (12.5)
Trauma	3 (7.5)
Cerebrovascular event	3 (7.5)
Intracranial mass	3 (7.5)
Sensory (due to low vision)	3 (7.5)
Congenital	2 (5)
Surgery for orbital mass	2 (5)
Sagging eye syndrome	1 (2.5)
Multiple sclerosis	1 (2.5)
Myasthenia gravis	1 (2.5)

The three most common etiology was thyroid eye disease (6 patients; 15%), followed by diabetes mellitus (5 patients; 12.5%), and hypertension (5 patients; 12.5%).

In 26 (65%) patients, the ocular deviation was caused by cranial nerve palsy. In 19 (47.5%) patients, cranial imaging was available. There was no significant difference in age between patients with paralytic and non-paralytic strabismus (69.19 ± 5.25 years vs. 71.71 ± 7.51 years, $p > 0.05$). The most common type of paralytic strabismus was due to the isolated sixth nerve palsy (12 patients; 30%), followed by isolated fourth nerve palsy (8 patients; 20%), isolated third nerve palsy (3 patients; 7.5%), combined third and sixth nerve palsies (1 patient; 2.5%), combined sixth and seventh nerve palsies (1 patient; 2.5%), and multiple cranial neuropathies (1 patient; 2.5%).

In five (12.5%) patients, the underlying cause of strabismus remained unidentified. Further, 10 (25%) patients were treated with prismatic glasses, whereas 7 (17.5%) patients received botulinum toxin injection.

Only 26 (65%) patients came to the clinic for the control visit, and the mean number of control visits was 2.46±2.01.

Moreover, 11 (27.5%) patients underwent surgery: 9 (22.5%) patients underwent one surgery, 1 (2.5%) patient underwent two, and 1 (2.5%) patient underwent three surgeries. Three of the patients were offered strabismus surgery, but they denied.

DISCUSSION

According to the demographic projections for the aging population worldwide, the global life expectancy as well as the number of individuals with a longer lifespan are increasing (5).

Binocular vision and eye movement disorders are common in the elderly (6). With the increase in age, there is an accumulation of age-related

systemic and/or ocular diseases. Chronic diseases are more common and tend to simultaneously occur in the elderly, thereby resulting in a phenomenon called multimorbidity (7). Comorbid conditions may also be suitable for the occurrence of acquired, particularly paralytic, strabismus.

In the present study, we evaluated the etiology and characteristics of ocular deviations in elderly patients.

Although strabismus is commonly reported and diagnosed in children, it is not restricted to childhood. Hashemi et al. systematically reviewed the global and regional prevalence of strabismus and showed that the estimated pooled prevalence of strabismus was 1.93%, whereas it was 1.23% for esodeviations and 0.77% for exodeviations (8). The heterogeneity of prevalence was significantly affected by age and WHO region; for example, exotropia was more frequent in patients aged ≥20 years compared with those aged <20 years and strabismus was more prevalent in two WHO regions: European Regional Office and South-East Asia Regional Office (8).

In the present study, the major complaint of the patients was diplopia. Double vision is an extremely disabling symptom that can affect the quality of daily life of patients. Kawai et al. investigated the clinical characteristics of patients aged ≥60 years who complained of binocular diplopia and found that the most common type of strabismus was esotropia due to orbital pulley disorder (9). They classified the causes of strabismus according to the type of deviation and demonstrated that orbital pulley disorder was the main reason for esodeviation, whereas it was convergence insufficiency for exodeviation, fourth nerve palsy for vertical deviation, and orbital pulley disorder and fourth nerve palsy in an equal frequency for combined deviation (9). In the present study, there was one patient with sagging eye syndrome caused by the abnormalities of the extraocular muscle bands, which are primarily induced by the aging process (10). Typically, the band between the lateral and superior recti becomes thin with the increase in age and results in the inferior displacement of the lateral rectus and eventually in esotropia (10).

Martinez-Thompson et al. investigated the incidence and type of new-onset strabismus in a cohort with a median age of 65 years and found that 86.2% exhibited diplopia as a presenting symptom and 68% exhibited horizontal deviation (1). In the present study, 65% of the patients exhibited isolated horizontal deviation. Moreover, in the study by Martinez-Thompson et al., the annual incidence of adult-onset strabismus was 54.1 cases per 100000 individuals, the peak incidence was during the eighth decade of life, and paralytic strabismus was the most frequent type of ocular misalignment (1). However, they included only adults aged ≥19 years who developed new ocular misalignment during the study period (1). Notably, in the present study, 67.5% of the patients were admitted to the strabismus clinic after more than 1 year of its occurrence, indicating that the elderly individuals do not prefer to seek treatment for strabismus either because it loses priority among other serious medical conditions or they do not believe that it can be cured. However, strabismus surgery in adults has demonstrated positive psychosocial implications as well as improved binocularity besides its cosmetic effect (11, 12).

Repka et al. reviewed strabismus among the aged fee-for-service Medicare beneficiaries, of which the patients aged ≥65 years constituted the largest cohort, and found that strabismus was diagnosed in 0.68% of the patients, with paralytic deviation being the most common type (2). They demonstrated that the strabismus diagnosis was increasing with age after 65 years and decreasing after 80-84 years (2).

Tamhankar et al. investigated the isolated cranial nerve (third, fourth, and sixth) palsies in a cohort of patients aged ≥50 years (13). The most common type was the sixth nerve palsy, and the median duration of diplopia was 14 days (13).

They suggested that cranial imaging is important at the initial examination because it can reveal the underlying etiology besides microvascular ischemia (13). In the present study, 19 (47.5%) patients underwent cranial imaging. However, we are unaware and unsure of the data regarding imaging in all patients. The patients who did not re-visit the clinic might have undergone examination and treatment at other clinics. In the present study, 65% of the patients exhibited paralytic strabismus and sixth nerve palsy was the most frequent.

Fang et al. showed that patients aged ≥65 years who underwent strabismus surgery because of diplopia as a leading complaint showed successful outcomes in their retrospective cohort and suggested that surgery should be considered a viable option for elderly patients (14). In the present study, 11 (27.5%) patients underwent surgery, whereas 3 patients declined surgery.

Jackson et al. investigated the psychosocial benefits of strabismus surgery in adults aged between 16 and 61 years and showed that it offers a significant improvement in psychosocial and physical adjustment following surgery (15). This result may emphasize the importance of the strabismus surgery from a psychological point of view for a patient who is uncomfortable with his/her physical appearance or body image, particularly during instances requiring an eye contact, although there was no separate analysis for the geriatric age group.

Coats et al. showed that strabismus surgery might be delayed by as long as 72 years in adults (16). The two most common reasons for the delay were as follows: surgery was never offered and surgery was offered but declined (16). They suggested that the delay can be avoided by educating the medical community to offer appropriate surgical intervention and the patients to seek a solution for their complaint as well as by increasing public awareness regarding strabismus (16).

Myasthenia gravis, one of the causes of ocular misalignment, might be underdiagnosed in elderly individuals and mistaken for stroke, Parkinsonism, or other neurological disorders (17, 18). One of the patients in the study was diagnosed with myasthenia gravis, which is not a common diagnosis in the elderly. However, its age at onset was shown to have a significant shift toward the older age (19).

The present study had certain limitations. The medical files were collected from the strabismus clinic of a hospital with tertiary referral center characteristics. This could cause a bias in case selection and the results cannot be extrapolated to all elderly patients with strabismus. Overall, 14 (35%) patients did not re-visit the strabismus clinic and we are unaware of their progress; we believe that some of them might have received a diagnosis and treatment elsewhere. Treatment outcomes were beyond the scope of the manuscript and were not incorporated in the data analysis. The study reflects the findings of a single strabismus clinic. Several patients aged ≥65 years may not have been referred to a strabismus clinic because other ocular and/or systemic disorders dominate their clinical picture and an ocular deviation loses its priority. Because the number of patients was limited, the sample was not stratified in subgroups according to the age as 65–69, 70–79, and ≥80 years. Despite its limitations, the present study provides supportive evidence that cranial nerve palsy is one of the most common causes of ocular deviation and for admittance to a strabismus clinic in elderly individuals.

One of the interesting findings of the present study was the number of patients lost to follow-up. A significant proportion of the patients failed to come to the clinic again for a control visit possibly because they did not desire to undergo general anesthesia or did not have the opportunity to be accompanied by their relatives to go to a hospital. All the aforementioned drawbacks should be taken into consideration. One possible

explanation is that several elderly individuals do not seek a surgical solution because of the general anesthesia risk, possibility of postoperative diplopia, and unsatisfactory surgical result. However, a remarkable portion of patients did not visit the strabismus clinic despite a nonsurgical option, such as prismatic glasses or botulinum toxin injection, was recommended.

Notably, there was a general reluctance among patients who were admitted to the strabismus clinic. Some patients denied surgery, whereas some failed to re-visit the clinic, although only follow-up was recommended without any intervention.

Considering the frequency of cranial nerve palsy as one of the leading causes of ocular misalignment in the geriatric population concurrent with systemic comorbidities, the results of the present study lend support to the consideration of strabismus, particularly recent-onset strabismus, as an emergency in this age group. On the other hand, strabismus can develop due to the worsening of a previously controlled latent deviation.

The results of the present study demonstrate that strabismus is observed in the elderly. The underlying condition may be potentially serious but treatable; therefore, particularly recent ocular deviations in the geriatric population should be carefully managed and ideally, in collaboration with other departments, such as neurology.

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CONFLICTS OF INTEREST

The authors of this article state that they have no conflict of interest.

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RESEARCH

SWALLOWING IN ELDERLY INDIVIDUALS: SILENT DYSPHAGIA RISK ASSESSMENT IN THE ENT OUTPATIENT CLINIC

Abstract

Introduction: Advancing age may cause deterioration of the cartilaginous and myoelastic structures of the larynx, leading to dysphagia. This study aimed to assess dysphagia and swallowing-related quality of life in elderly individuals presenting to the ENT outpatient clinic with no dysphagia complaint.

Materials and Method: Among 1829 patients who visited the ENT outpatient clinic between February 2017 and September 2018, 745(379 females, 366 males; mean age 74.27±6.32 years) volunteered to participate. These individuals had no swallowing problems or any disease that could affect swallowing, drug use, neurological disorder or history of head and neck surgery. The patients were assessed using swallowing-related quality of life scale and Eating Assessment Tool-10.

Results: According to the Eating Assessment Tool-10 scores, 550 patients(mean age 72.00±4.45 years) had normal swallowing and 195(mean age 80.68±6.44 years) had dysphagia. There was a significant difference regarding age and swallowing-related quality of life scale scores were statistically significant between the normal swallowing and dysphagia groups. Regarding diagnosis at admission, no significant intergroup differences were observed. On assessing the distribution of both scale scores according to the age groups (65–69, 70–79, 80–89, and 90–99 years), significant differences were observed among all groups. There was a significant correlation between increased scores and increasing age.

Conclusion: Dysphagia is a common problem in older individuals. However, most patients with dysphagia do not visit physicians for this problem. It should be remembered that swallowing problems are often diagnosed when patients present to outpatient clinics for other complaints.

Keywords: Dysphagia; Aged; Deglutition disorders

ARAŞTIRMA

YAŞLI BİREYLERDE YUTMA: KBB POLİKLİNİĞİNDE SESSİZ DİSFAJİ RİSK DEĞERLENDİRMESİ

Öz

Giriş: İlerleyen yaş larinksin kıkırdak ve miyoelastik yapılarının bozulmasına ve disfajiye neden olabilir. Bu çalışma, KBB polikliniğine başvuran disfaji şikayeti olmayan yaşlı bireylerde yutma güçlüğü ve yutma ile ilişkili yaşam kalitesini değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Şubat 2017-Eylül 2018 tarihleri arasında KBB polikliniğine başvuran 1829 hasta arasından 745'i (379 kadın, 366 erkek; ort. Yaş 74.27±6.32 yıl) çalışmaya gönüllü oldu. Bu kişilerde yutma problemi veya yutmayı etkileyebilecek herhangi bir hastalık, ilaç kullanımı, nörolojik bozukluk veya baş boyun bölgesine ameliyat öyküsü mevcut değildi Hastalar, yutma ile ilişkili yaşam kalitesi ölçeği ve Yeme Değerlendirme Aracı-10 kullanılarak değerlendirildi.

Bulgular: Yeme Değerlendirme Aracı-10 puanlarına göre 550 hasta (ort. Yaş 72.00±4.45 yıl) normal yutma, 195 hastada (ort. Yaş 80.68±6.44 yıl) disfaji vardı. Yaş ve yutma ile ilişkili yaşam kalitesi ölçek puanları açısından normal yutma ve yutma güçlüğü grupları arasında istatistiksel olarak anlamlı fark saptandı. Başvuru sırasındaki tanı açısından gruplar arasında anlamlı bir fark gözlenmedi. Her iki ölçek puanının da yaş gruplarına göre dağılımını değerlendirirken (65-69, 70-79, 80-89 ve 90-99 yaş), tüm gruplar arasında anlamlı farklılıklar gözlendi. Skorların artması ile yaşın artması arasında anlamlı bir ilişki vardı.

Sonuç: Disfaji yaşlı bireylerde sık görülen bir sorundur. Ancak, disfajili hastaların çoğu bu sorun için hekimleri ziyaret etmemektedir. Başka şikayetlerle polikliniğe başvuran hastalarda yutma sorunlarının sıklıkla teşhis edildiği akılda tutulmalıdır

Anahtar sözcükler: Disfaji; Yaşlı; Yutma bozuklukları

INTRODUCTION

Difficulty in swallowing, known as dysphagia, is one of the common problems faced by elderly individuals, and its increased incidence is increasing in the aging population (1.) Although the prevalence of dysphagia increases with age, it has been reported to exist in a wide rate range of 11%–68% (1,2). The most significant outcomes of dysphagia in the elderly are morbidities such as malnutrition and dehydration and aspiration pneumonia, which results in mortality in almost half of the patients (3). Furthermore, studies have reported that almost all pneumonias observed in the elderly are related to aspiration (4).

The most common causes of dysphagia in the elderly are neurological diseases such as stroke, Parkinson's disease, and dementia, which are commonly observed in the elderly (3). Oropharyngeal dysphagia (OD) associated with these diseases is the primary cause of most aspirations. Dysphagia may also be observed as a result of aging. Presbyphagia is a term used for the structural and physiological changes related to aging that are observed in all phases of swallowing (5). Presence of dysphagia in up to 30% of the elderly individuals living independently and not necessarily leading to dysphagia primarily has been reported (1,2). However, no specific incidence rate has been reported. The symptoms of OD related to old age are often accepted as age-related changes, for which medical advice is usually not sought, and may be compensated by the patient because they develop slowly. Notably, the patient may be aware of the situation because of the compensatory mechanisms used, such as reducing the volume and changing the type of food (6). Lack of awareness and/or using compensatory mechanisms may not necessarily lead to complications that increase the risk of aspiration-related morbidity and mortality. Nonetheless, eating and swallowing is a social behavior, and the patient's quality of life may be severely affected.

Although dysphagia due to comorbidities such as neurological disease accompanied by age is well defined, dysphagia in healthy elderly who had no complaint dysphagia and who had no disease that may cause dysphagia is not known exactly (7,8).

Otorhinolaryngology is the branch of medical science that deals with swallowing. Therefore, it is the most important and primary branch that can intervene in case of lack of awareness in both the elderly and the clinicians regarding the risk of dysphagia.

Therefore, we need to ask ourselves the following questions considering the increase in the number of admissions to our clinics, especially that of the elderly:

1) Is there any risk of OD that may lead to aspiration in the elderly patient who has presented to our clinic with a complaint other than that of difficulty in swallowing?

2) Is there an increase in the risk with the increase in age?

3) Could the presence of OD risk alone affect the quality of life, even though there is no symptom or complaint?

This study aimed to investigate the OD risk in elderly patients presenting to our clinics with complaints other than symptoms/findings of dysphagia and demonstrate the effect of the relationship between the increase in age and the quality of life.

MATERIALS AND METHOD

Study design

The study was conducted in a cross-sectional design comprising 800 patients aged ≥65 years who presented to our ear-nose-throat (ENT) outpatient clinics with complaints other than difficulty in swallowing.

Participants

The participants included patients aged □65

years, who could sit properly, communicate, had the mental wellness for cooperation, and had no the primary complaint of difficulty in swallowing. Those with known dysphagia, speaking disorder, limited cooperation and orientation, a history of head-neck surgery, malignancy, diagnosed psychiatric disorder, progressive or non-progressive neurological disease that may affect swallowing, gastrointestinal system disease, ear, nose and throat disease which may affect swallowing or those with symptoms/findings of esophageal dysphagia were excluded.

Patients were informed about the study, and their written consents were obtained at the beginning of the study. The approval was obtained from the local Ethical Board of the hospital, and the study was conducted accordant with the principles of the Helsinki Declaration.

Data Collection

Demographic characteristics including age, gender, and diagnosis on admission were recorded.

Swallowing Assessments

1. Eating Assessment Tool-10 (EAT-10) (9)

The Eating assessment tool (EAT-10) is a scale that evaluates dysphagia and contains 10 questions with each question scored between 0 and 4 (no problem to severe problem). The total EAT-10 score is calculated by adding the score obtained in each question, with the total score ranging between 0 and 40. A score of 3 or higher was considered as risk of OD.

2. Swallowing-related quality of life scale (SWAL-QOL) (10)

The swallowing-related quality of life scale (SWAL-QOL) is used to evaluate the effect of swallowing disorders on the quality of life. This scale contains 44 questions on eating disorders, duration of eating, appetite, food selection, communication, anxiety, mental health, social functioning, fatigue, and sleep. Each question is scored between 1 (worst) and 5 (best). Each field may be assessed separately. The total score was used in our study.

Study Protocol

All participants were assessed using EAT-10 and SWAL-QOL. They were grouped as no OD and OD risk based on their EAT-10 scores, and the parameters were compared between groups. The correlation between significant parameters was investigated. The subjects were grouped as 65–69 years (group 1), 70–79 years (group 2), 80–89 years (group 3), and 90–99 years (group 4) to investigate any age-related effects and their EAT-10 and SWAL-QOL scores were compared.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS 22.0 for Windows) software package was used in the analysis of the data. In descriptive statistics, the data were expressed as the mean ± standard deviation for continuous variables, and as frequencies and percentages (%) for nominal variables. Normality was evaluated using the Kolmogorov-Smirnov test (all parameters were normally distributed). Based on their EAT-10 scores, the patients were divided into two groups: dysphagic and normal swallowing. Significant intergroup differences were analyzed using t-test and ?2 test. Correlations between the age, SWAL-QOL, and EAT-10 were examined using the Pearson correlation coefficient. Logistic regression analysis was performed to examine the associations between potential independent predictors (age and SWAL-QOL scores) and EAT-10 scores (dependent variable). Based on the age, participants were divided into four groups as 65–69 years (group 1), 70–79 years (group 2), 80–89 years (group 3), and 90–99 years (group 4). Evaluation parameters of age groups were analyzed using analysis of variance test. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 745 patients, 366 (50.9%) were females and 366 (49.1%) were males. The mean patient age was

74.27 ± 6.32 years. The patient characteristics are presented in Table 1.

Table 1. Demographic and clinical characteristics of the patients aged ≥65 years at the initial presentation to the strabismus clinic

Parameters	N=745 (mean±SD), n(%)
Age (year)	74.27±6.32
Gender	
Female	379 (50.9)
Male	366 (49.1)
Diagnosis	
Hearing loss	239 (32.1)
Cerumen	84 (11.3)
Acute pharyngitis	85 (11.4)
Chronic otitis media (COM)	43 (5.8)
Epistaxis	20 (2.7)
Common cold	50 (6.7)
Allergic rhinitis	41 (5.5)
Acute sinusitis	28 (3.8)
Tinnitus	72 (9.7)
Otitis externa	45 (6.0)
Vertigo	21 (2.8)
Nasal polyp	11 (1.5)
Acute tonsillitis	6 (0.8)
EAT-10	1.95±1.60
Swal-Qol	52.81±14.92

SD: standard deviation; EAT-10: Eating Assessment Tool-10; Swal-Qol:Swallowing Quality of life

Based on the EAT-10 scores, 550 (73.8%) patients had normal swallowing with the mean age of 72.00 ± 4.45 years, and 195 (26.2%) patients had OD risk with the mean age of 80.68 ± 6.44 years. Regarding the diagnosis on admission, no significant intergroup differences were determined (p = 0.121). The age and Swall-QoL scores were statistically significant between the normal swallowing and OD risk groups (p=0.001) (Table 2).

The correlation and regression analyses between age and EAT-10 and SWAL-QOL scores, which showed significance, and the distribution of scale outcomes for ages are demonstrated in Tables 3–5.

Comparison of EAT-10 and SWAL-QOL scores of different age groups showed statistically significant differences among all groups (all of them, p = 0.001).

Accordingly, the correlation between age and each score of EAT-10 and SWAL-QOL scales were significant, and an increase in the EAT-10 and SWAL-QOL scores were noted with the increase in age (p = 0.001). Therefore, age was defined as an independent factor that affected the EAT-10 scores.

DISCUSSION

This study aimed to investigate OD risk in elderly patients presenting to the ENT clinics with complaints other than difficulty in swallowing and to demonstrate the effect of the relationship between the increase in age and the quality of life. We observed that regardless of the clinical diagnosis, with advancing age, the OD risk was increased and the quality of life was impaired.

Like the changes in all other systems of the body, swallowing function also changes with age. Age-related structural and physiological changes cause a predisposition to dysphagia, just like other age-related diseases. Reduction in the mass of the muscles involved in swallowing and connective tissue elasticity results in loss of strength and movement (11-13). These age-related changes have negative effects on the passage of food from the mouth to the stomach effectively and safely. Generally, a deceleration is observed in the swallowing process with aging (12). More time is required for food preparation in the oral phase, the swallowing reflex trigger is delayed, and all transit mechanisms are decelerated. These changes may seem non-significant and may result in no symptoms, but they may be cumulative

Table 2. Distribution of parameters according to the EAT-10 scores.

	Normal swallowing (n=550) (mean±SD), n(%)	Dysphagia (n=195) (mean±SD), n(%)	P
Age (year)	72.00±4.45	80.68±6.44	0.001
Gender			
Female	279 (50.7)	100 (51.3)	0.894
Male	271 (49.3)	95 (48.7)	
Diagnosis			
Hearing loss	171 (31.1)	68 (34.9)	
Cerumen	59 (10.7)	25 (12.8)	
Acute pharyngitis	70 (12.7)	15 (7.7)	
COM	32 (5.8)	11 (5.6)	
Epistaxis	15 (2.7)	5 (2.6)	
Common cold	41 (7.5)	9 (4.6)	0.121
Allergic rhinitis	37 (6.7)	4 (2.1)	
Acute sinusitis	21 (3.8)	7 (4.6)	
Tinnitus	62 (11.3)	10 (5.1)	
Otitis externa	36 (6.5)	9 (4.6)	
Vertigo	0	21 (10.8)	
Nasal Polyp	0	11 (5.6)	
Acute tonsillitis	6 (1.1)	0	
Swal-Qol	47.36±12.53	68.20±9.30	0.001
EAT-10	1.19±0.76	4.11±1.37	0.001

SD: standard deviation; EAT-10: Eating Assessment Tool-10; Swal-Qol:Swallowing Quality of life

and lead to increased penetration frequency of the swallowed bolus into the upper airways and to increasing amount of residues observed after swallowing. When age-related sensorimotor changes are also added to the aforementioned, it contributes to clinically significant dysphagia and related complications (14). In our study, we observed the risk of OD in one-fourth of patients older than 65 years regardless of the diagnosis on admission. Furthermore, we observed that this risk positively correlated with the increase in the age of the patients.

Our study did not include patients with a complaint of dysphagia or those who had any neurological/non-neurological disease that may lead to dysphagia. Therefore, neither the patients nor the clinicians had any concern regarding dysphagia or its complications, such as malnutrition, dehydration, pneumonia, or even death.

Studies in the literature have reported that the incidence of pneumonia is exacerbated, the functional loss is increased, and the quality of life is further impaired with advancing age of the patient (3,15). Aspiration-related pneumonia and pneumonia-related mortality rates have been demonstrated to increase with age (3,16-18). To our knowledge, no study has investigated the age-related changes and the presence of age-related diseases together. However, nutritional studies have reported 10%–15% malnutrition owing to

Table 3. Distribution of EAT-10 and Swal-Qol scores according to the age groups.

	65-69 years (n=222) (mean±SD)	70-79 years (n=368) (mean±SD)	80-89 years (n=141) (mean±SD)	90-99 years (n=14) (mean±SD)
EAT-10	0.65±0.98	1.98±1.06	3.51±1.39	6.21±1.67
Swal-Qol	36.57±9.41	56.11±9.44	67.17±9.03	79.05±6.92

SD: standard deviation; EAT-10: Eating Assessment Tool-10; Swal-Qol:Swallowing Quality of life

reduction or deceleration in nutritional intake and change in nutrients in community-dwelling elderly, even in the absence of known dysphagia (19). We believe that this low nutritional situation reduces the functional capacity of the patient, thereby impairing the quality of life, with age and age-related changes having indirect effects.

Although our study was a wide-scale study, it had some limitations. Flexible fiberoptic endoscopy and videofluoroscopy are the conventional methods used to diagnose OD; however, scales, which are rapid, cheap, easy to use, and non-invasive, are used widely to identify patients for further examination (20,21). In our study, the EAT-10 scale test was used because of the high number of patients and ease of applicability in the outpatient clinic environment, and hence, the gold standard methods were not used. Nonetheless, we believe that further extensive research on the elderly population using the conventional techniques will make the outcomes of our study more understandable.

In conclusion, age is an independent factor for OD risk in elderly people. In clinical practice, the ENT department is capable of diagnosing dysphagia using the flexible fiberoptic endoscopy method, which we believe should be considered by the clinicians practicing social preventive medicine to assess elderly patients with no complaint of swallowing difficulty.

Conflict of Interest. The authors have no conflict of interest to declare.Patients who did not undergo curative resection for colorectal cancer, those treated with Hartmann procedure or transanal local resection, those treated only with deflective stoma, those with missing data, and those who were operated under emergency conditions were excluded from the study. According to the American Joint Commission on Cancer (AJCC) TNM staging (13), patients with middle and lower rectal carcinoma other than T1 received neoadjuvant chemoradiotherapy (CRT) and total

Table 4. Correlations between the age, Swal-Qol and EAT-10 scores.

	Age (r/p)	EAT-10 (r/p)	Swal-Qol (r/p)
Age		0.721/0.001	0.763/0.001
EAT-10	0.721/0.001		0.791/0.001
Swal-Qol	0.763/0.001	0.791/0.001	

r: correlation coefficient, EAT-10: Eating Assessment Tool-10; Swal-Qol:Swallowing Quality of life

Table 5. Regression analysis of significantly correlation.

	B	SE	95%CI (lower-upper)for B	p
Age	0.071	0.008	0.055-0.088	0.001
Swal-Qol	0.062	0.004	0.055-0.069	0.001

OR: odds ratio, CI: coefficient interval, SE: Standard error

mesorectal excision was performed 8–10 weeks after CRT. A protective ileostomy was routinely performed following anastomosis below the peritoneal reflection in patients with rectal tumor who received neoadjuvant CRT. The decisions were made on a case-by-case basis for the remaining patients with upper rectal and colonic tumors considering their general condition and depending on technical issues encountered both during anastomosis and during the perioperative period. In our study, all patients who underwent surgery for colorectal cancer under elective conditions underwent resection and anastomosis with or without stoma.

Outcome measure and other variables

Patients included in the study were divided into two groups: patients aged <65 years (Group 1) and those aged ≥65 (Group 2). Demographic characteristics, perioperative risks, diseased colonic segment, neoadjuvant CRT, and surgical procedure (laparoscopic/open) were evaluated between both groups. The primary endpoint of the study was AL that developed within 30 days postoperatively. The secondary endpoint was AL-related mortality within 30 days postoperatively.

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, New

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RESEARCH

VITAMIN D IS ASSOCIATED WITH COGNITIVE STATUS IN PATIENTS WITH ALZHEIMER'S DISEASE

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Abstract

Introduction: Previous studies have reported an association between low 25-hydroxyvitamin D (25(OH)D) levels and cognitive impairment. However, this association has not been reported in Turkish patients with cognitive impairment. We investigated this relationship in Turkish patients diagnosed with Alzheimer's disease (AD).

Materials and Method: Seventy-two patients with a diagnosis of "Probable AD" were included in the study. Demographic and disease specific characteristics were recorded. Cognitive performance was assessed using the Mini-mental State Examination (MMSE). Patients were categorized into two groups with regard to their 25(OH)D levels based on the recommended cut-off value (30 ng/ml) for 25(OH)D insufficiency. Association between 25(OH)D levels and MMSE scores was assessed using a regression model taking probable confounding factors into account.

Results: Sixty-nine patients were included in the final analysis. Patients with 25(OH)D levels higher than 30 ng/ml performed (n=18) significantly better in MMSE than the group with lower values (n=51) (p=0.027). Subsequently, the multiple linear regression analysis showed a significant association between 25(OH)D levels and MMSE scores; this association was independent of the confounding effects of age, gender, education, disease duration, anti-dementia medication and depressive state (B= 2.81, p=0.04).

Conclusion: Our results support that low 25(OH)D levels are associated with worse cognitive performance in Turkish patients with AD. Larger population-based studies are required to clarify this relationship in Turkish population not only in patients with AD, but also in individuals with mild cognitive impairment and healthy elderly.

Keywords: Alzheimer disease; Vitamin D; Aged

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ARAŞTIRMA

ALZHEİMER HASTALIĞINDA VİTAMİN D'NİN KOGNİTİF DURUM İLE İLİŞKİSİ

Öz

Giriş: 25-hidroksivitamin D (25(OH)D) yetersizliğinin bilişsel bozuklukla ilişkili olduğu önceki çalışmalarda bildirilmiştir. Ancak bu ilişkiyi bilişsel işlevlerde yıkımı olan Türk Alzheimer hastaları örnekleminde inceleyen bir çalışmaya ulaşılabilen literatür bağlamında rastlanmamıştır. Bu çalışmada, Türkiye'de Alzheimer hastalığı (AH) tanısı almış hastalarda bu ilişkiyi araştırmak amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmaya "Olası AH" tanısı almış 72 hasta dahil edilmiştir. Hastaların demografik ve hastalıkla ilişkili özellikleri kayıt altına alınmıştır. Bilişsel durum değerlendirmesi için Standardize Mini Mental Durum Testi (SMMDT), depresyon taraması için ise Geriatrik Depresyon Ölçeği (GDÖ) kullanılmıştır. Hastalar 25(OH)D yetersizliği için daha önce önerilmiş olan 30 ng/ml düzeyine göre iki gruba ayrılmıştır. 25(OH)D düzeyi ve SMMDT puanları arasındaki ilişki, regresyon modeli ile hastaların bilişsel performanslarına etki edebilecek olası diğer faktörler de göz önüne alınarak değerlendirilmiştir.

Bulgular: Toplamda 69 hasta analize alınmıştır. 25(OH)D düzeyi 30 ng/ml ve üzeri olan grup (n=18) SMMDT'nde düsük değerleri olan gruba oranla (n=51) anlamlı olarak daha başarılı performans göstermiştir (p=0.027). Bir sonraki aşamada uygulanan çoklu lineer regresyon analizi sonuçları, 25(OH)D düzeyi ile SMMDT puanları arasında yaş, cinsiyet, eğitim, hastalık süresi, tedavi ve depresif durumun etkilerinden bağımsız anlamlı bir ilişki olduğunu göstermistir. (B=2.81, p=0.04).

Sonuç: Elde edilen sonuçlar AH tanısı almış Türk hastalarda düşük 25(OH)D düzeyinin düşük bilişsel performans ile ilişkili olduğuna işaret etmektedir. Türk toplumunda bu ilişkiyi sadece AH'nda değil, hafif bilişsel bozukluğu olan kişilerde ve sağlıklı yaşlılarda da araştıracak geniş ölçekli toplum bazlı çalışmalara ihtiyaç vardır.

Anahtar sözcükler: Alzheimer hastalığı; Vitamin D; Yaşlı

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by decline in cognitive functions, especially loss of episodic memory (1,2). As the leading cause of dementia, the global prevalence of AD is estimated to quadruple over the following decades, reaching 115.4 million by 2050 (1), which is expected to have a huge socioeconomic impact. Despite considerable efforts, no treatment that could slow or alter the disease progression has yet been found. Thus, currently, detection and treatment of the modifiable causes of AD are of utmost importance.

Several modifiable medical or lifestyle risk factors for AD such as diabetes, hypertension, physical inactivity, poor education in the early phase of life and socioeconomic status have been reported in various studies (2). Following the improvement of these factors over the past decades a decline in the prevalence of AD was achieved especially in the developed countries (3). It has been reported that 25-hydroxyvitamin D (25(OH)D) insufficiency may also be one of these risk factors. Despite controversy, the majority of reports in literature including large population-based studies favor the association between low 25(OH)D levels and cognitive impairment (4).

A prevalence study has reported that 33% of the Turkish elderly population has 25(OH) D deficiency (5). However, to the best of our knowledge no study has evaluated the association between 25(OH)D levels and cognitive impairment in Turkish elderly individuals. Thus, in this study we set out to investigate this relationship in Turkish patients who were diagnosed with AD

MATERIALS AND METHOD

Patients and clinical assessments

Seventy-two patients who fulfilled the criteria for "probable AD with increased level of certainty" according to the latest diagnostic guideline (6) were recruited from the outpatient clinic of Department of Neurology between January and November 2018. Demographic and disease specific data including education, disease duration (based on symptom onset) as well as anti-dementia medication (Donepezil, Rivastigmine, Memantine) were collected. Depressive state was evaluated using the Turkish version of the Geriatric Depression Scale (GDS). Cognitive performance of the patients was assessed using the Turkish version of the Mini-mental State Examination (MMSE). Eleven patients were assessed by the Montreal Cognitive Assessment (MoCA) for whom the scores were converted to MMSE using the suggested conversion table (7). Based on the previously recommended cut-off value (30 ng/ml) for 25(OH)D insufficiency (8), the patients included in the study were categorized into two groups (25(OH)D levels ≥30 ng/ml and <30 ng/ml). All procedures were performed in accordance with the Declaration of Helsinki, and an informed written consent was obtained from all participants or legal representatives.

Biomaterial collection

Blood levels of 25(OH)D were analyzed using the standard operating procedure using high-performance liquid chromatography (Thermo-Finnigan, Waltham, US) along with the ClinRep HPLC 25(OH)D kit (RECIPE Chemicals & Instruments GmbH, Munich, Germany). Samples were injected in a mobile phase, which had a flow rate of 1.0 ml/min. To determine of the within-run precision, the samples were measured in duplicate. The estimated average coefficient of variation was 4.8%.

Statistical analyses

Descriptive and quantitative data are given as mean and standard deviation. Demographic data and the MMSE scores of the two groups were compared using student's t-test (for continuous variables) or a chi-square test (for categorical

variables). A multiple linear regression analysis was further performed to assess the association between 25(OH)D levels and the MMSE scores; age, sex, education, GDS, disease duration and anti-dementia medication were considered as covariates. A hierarchical entry method was used in which the covariates were added in the first step following the inclusion of 25(OH)D groups in the second step. The significance threshold was set to $p < 0.05$. SPSS Statistics 21.0 sofware package (SPSS Ltd., Chicago, IL, US) was used for the analysis.

RESULTS

Of the 72 patients recruited in the study, 3 patients were excluded due to missing 25(OH)D values. The remaining 69 patients were divided into two groups: patients with 25(OH)D levels ≥30 ng/ml (n=18) and <30 ng/ml (n=51). Age, sex, education, depressive state, disease duration or anti-dementia medications of the two groups were similar (Table-1). Student's t-test showed that regarding MMSE, the performance of patients with 25(OH)D levels ≥30 ng/ml was significantly better than that of those with levels <30 ng/ml (p=0.027).

Additionally, multiple linear regression was performed to predict the MMSE scores based on age, gender, education, GDS, disease duration, anti-dementia drug usage, and 25(OH)D groups. A significant regression equation was found ($F(7,60) = 5.345$; $p < 0.001$) in the first step with an R2 of 0.38. With the inclusion of 25(OH)D groups in the second step, the R2 value increased to 0.43 ($F(8,59) = 5.459$; $p < 0.001$). The MMSE scores of the patients decreased by -0.24 points for each year increase in age and -0.28 points for each point of increase in GDS. On the other hand, the MMSE scores increased by 1 point for 0.49 additional year of education. No significant effect was found with gender, disease duration or drug usage. Having controlled these confounding variables, patients with 25(OH)D levels ≥ 30 ng/ml scored 2.81 points more than the patients with levels < 30 ng/ml. The details of the regression results are shown in Table-2.

DISCUSSION

The results of our study showed that patients with

Table 1. Demographic and disease characteristics of the groups.

	25(OH)D < 30ng/ml (n=51)	25(OH)D ≥ 30ng/ml (n=18)	P value
Age [years], mean (SD)	76.6 (7.8)	75.3 (5.0)	0.46
Male gender [%]	41.2	44.4	0.81
Education [years], mean (SD)	4.9 (4.1)	5.2 (3.6)	0.76
Disease duration [months], mean (SD)	28.8 (28.8)	26.6 (18.6)	0.76
Geriatric Depression Scale, mean (SD)	10.5 (6.5)	8.9 (6.2)	0.40
AChE-inhibitor usage [%]	41.2	44.4	0.81
Memantine usage [%]	20	38.9	0.11
Mini-Mental State Examination , mean (SD)	17.4 (6.0)	20.9 (4.8)	0.027*

SD, Standard deviation; AChE, Acetylcholinesterase * P value < 0.05

AD whose serum 25(OH)D levels lower than 30 ng/ml performed worse in MMSE compared to patients with levels ≥30 ng/ml. Importantly, this result was independent from the confounding effects of age, gender, education, depressive state, disease duration or anti-dementia medication. As expected, we also found a negative relationship of age and depression scores in GDS with the MMSE scores. Likewise, an increase in education level positively correlated with the MMSE scores.

An association between 25(OH)D levels and cognition has been investigated in several cross-sectional studies in adolescents (9), elderly population (10) and individuals diagnosed with cognitive impairment (11). Most of these studies have reported a concordance between 25(OH) D levels and cognitive status. Similarly, the vast majority of the longitudinal studies have also described a close association (12,13), only in contrast to few which have found no such relationship (14). A study conducted in Turkey with 104 neurologically healthy women also reported no association (15). Despite various negative results, the accumulated evidence from the major studies have indicated that 25(OH)D deficiency is an independent risk factor for cognitive decline and dementia (4,13). Nevertheless, interventional studies and randomized-controlled trials with 25(OH)D supplementation have provided limited information due to conflicting results which may be attributed to differences in the recruited population, baseline 25(OH)D levels, supplement doses or follow-up period (16). Even if improvement in cognition was not observed following 25(OH)D supplementation, that may indicate that 25(OH) D, being a risk factor, may play a role in the pathological process, and its augmentation does not alter the neurodegenerative damage which has already occurred.

Our results in AD patients are consistent with those obtained in previous research showing that 25(OH)D is indeed associated with cognitive impairment. In this study, the MMSE scores were also significantly correlated with age, education

Table 2. Regression coefficients of multiple linear regression in the second step.

	B	SE – B	β (95 % CI)	P value
Constant	38.6	7.3	-	-
Age	-0.24	0.09	-0.29 (-0.42 – -0.06)	0.008**
Gender	-0.10	1.6	0.008 (-3.2 – 3.04)	0.95
Education	0.49	0.2	0.33 (0.08 – 0.89)	0.019*
Geriatric Depression Scale	-0.28	0.1	-0.30 (-0.49 – - 0.07)	0.011*
Disease duration	0.003	0.03	0.02 (-0.05 – 0.05)	0.89
AChE-inhibitors	0.006	1.4	0 (-2.9 – 2.9)	1.00
Memantine	-0.89	1.6	-0.07 (-4.1 – 2.3)	0.58
25(OH)D Groups	2.81	1.4	0.21 (0.08 – 5.5)	0.044*

B, Regression coefficient; SE, Standard error; β, Beta value; CI, Confidence interval; AChE. Acetylcholinesterase; 25(OH)D, 25-hydroxyvitamin D
* P value < 0.05, ** P value < 0.01

and depressive state as anticipated. However, no significant association with disease duration was observed (Table-2); this could be related either to the shared variance between disease duration and other included factors or to the information bias generated from determining the disease duration based on symptom onset. Although collected in a uniform fashion, the information was extracted from subjective patient history, which is subjective in nature.

An additional issue that should be taken into account is the inconsistency across studies with regard to the cut-off value for the definition of 25(OH)D deficit. Some studies applied cut-off values at 20 ng/ml (50 nmol/l) and 10 ng/ml (25 nmol/l) to define 25(OH)D insufficiency and deficiency, respectively (12–14). However, ≥ 30ng/ml (≥ 75 nmol/l) was suggested as the adequate level of 25(OH)D by Holick et al., given that the parathyroid hormone levels do not taper down at values lower than 30 ng/ml (8). Therefore, we adapted this cut-off value as the optimal 25(OH)D level and regarded lower values as 25(OH)D insufficiency, which was also recommended by the task force of "Vitamin-D and Cognition in Adults" (17) and used in previous studies (18). Additional analyses with a cut-off value of <10 ng/ml with a definition of 25(OH)D deficiency was not performed due to extreme imbalance between group sizes (data not shown).

The pathophysiological role of 25(OH)D in brain has been demonstrated in several non-human studies. The presence of the 25(OH)D receptor in the brain has been shown, through which 25(OH)D probably exerts its antioxidant effects against glutamate-related mitochondrial neurotoxicity (19). Increase in amyloid clearance has also been detected with overexpression of 25(OH)D receptor (20). Additionally, 25(OH)D is involved in the synthesis of neurotrophic factors such as neurotrophin or nerve growth factor, which mediates growth and reduces the age-related inflammation in the hippocampal region (21). Furthermore, 25(OH)D regulates the expression of neurotransmitters such as acetylcholine, dopamine or serotonin and acts on voltage-gated calcium channels in the brain, thereby modulating calcium-related homeostasis (22). Furthermore, 25(OH)D has been shown to enhance the production of nitric oxide and provide protection against endothelial dysfunction and microvasculopathies (23). The risk for retinopathy, nephropathy and cerebrovascular diseases has been shown to increase in the presence of 25(OH)D deficiency (24), which in turn, is in accordance with the finding that low 25(OH)D levels are associated with not only AD but also vascular dementia (12). These studies elucidate the biological background of the clinical findings that suggest a crucial role of 25(OH)D in the pathophysiological mechanisms leading to a cognitive decline and recommend close monitoring of 25(OH)D levels in elderly individuals (17).

Several limitations of the current study need to be discussed. The effects of age, gender, education, depressive state, disease duration and anti-dementia medication were controlled by including these confounding factors in the regression model; however, additional potential confounders such as calcium and cholesterol levels, kidney functions, body mass index, smoking or alcohol intake, APO-E genotype, as well as socio-economic status, nutrition problems related with disease stage, systemic diseases such as diabetes or heart failure were not assessed in this study. Moreover, cognitive assessment of the patients participating in this study was performed using only MMSE, which does not reveal the details of the cognitive domains. Some previous studies have reported a selective association between 25(OH)D levels and cognitive tasks such as trail making test, digit span, and immediate word recall (25), which could not be tested in this study. Conversion of the MoCA scores into MMSE scores in 11 patients could have also added a bias, although we applied the conversion table designed for patients with

cognitive impairment. The relatively small sample size and the retrospective design are additional shortcomings of the present study.

In conclusion, we showed that patients with AD who had optimal (≥ 30ng/ml) serum 25(OH)D levels exhibited higher MMSE scores than those with inadequate 25(OH)D levels, thereby confirming the association of 25(OH)D concentrations and cognition in Turkish patients with AD. It should also be noted that this association does not imply any causality considering the cross-sectional nature of the study. Given that approximately one third of the elderly population in Turkey has 25(OH) D deficiency (5), the magnitude of the impact of 25(OH)D deficiency on cognition warrants further investigation in Turkish patients with cognitive impairment as well as in healthy elderly adults in future longitudinal studies with larger samples and strict confounder assessments.

CONFLICT OF INTEREST

The authors declare no conflict of interest

FINANCIAL DISCLOSURE

Nothing to report

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RESEARCH

TIME BISECTION ABILITY IN SUPRA-SECONDS IS PRESERVED DURING HEALTHY AGING

Abstract

Introduction: Interval timing requires cognitive resources such as attention, long-term memory, and working memory. Unfortunately, these functions deteriorate with aging. Changes in time perception are reported in healthy aging, in addition to several different neuropsychiatric disorders. Although age-related changes in time perception have been amply described in the literature, the actual underlying mechanisms remain controversial.

Materials and Method: This study included a total of 33 young (mean age = 23.31 years) and 33 old (mean age = 67.63 years) individuals who performed a time bisection task with a range of 1.25-2.5 seconds. The experimental design was strictly controlled to minimize the effects of age-related declines in cognitive functions. An additional psychometric measurement related to the subjective passage of time was also assessed.

Results: A Mann-Whitney U test was conducted with the bisection point, Weber ratio, and difference limen as the dependent variables. The young and old participants showed similar time bisection performances ($p \geq 0.05$). However, the verbal expression of the subjects indicated that time generally passes faster for old individuals whereas old participants expected the next hour to pass slower for them than did their younger counterparts ($p \leq 0.05$).

Conclusion: It was demonstrated that the perception of time is preserved with aging in the supra-second range when cognitive demands are minimized by reducing task complexity.

Keywords: Aging; Time perception

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ARAŞTIRMA

SANİYE ÜSTÜNDE SÜRE AYRIŞTIRMA YETENEĞİ SAĞLIKLI YAŞLANMADA KORUNMAKTADIR

Öz

Giriş: Aralık zamanlama, dikkat, uzun süreli bellek ve çalışma belleği gibi bilişsel kaynakların kullanılmasını gerektirmektedir. Maalesef, bu işlevler yaşlanmayla birlikte bozulmaktadır. Zaman algısındaki değişiklikler sağlıklı yaşlanmanın yanı sıra çeşitli nöropsikiyatrik bozukluklarda da görülmüştür. Her ne kadar zaman algısındaki yaşa bağlı değişiklikler literatürde fazlasıyla bildirilmiş olsa da, asıl altta yatan mekanizmalar tartışmalıdır.

Gereç ve Yöntem: 33 genç (ortalama yaş = 23,31) ve 33 yaşlı (ortalama yaş = 67,63) gönüllü 1,25-2,5 saniye aralığında bir süre ayrıştırma görevi yapmak için çalışmaya katılmıştır. Deney özellikle bilişsel işlevlerin yaşa bağlı düşüşlerinin etkisini en aza indirmek için tasarlanmıştır. Psikometrik ölçümlere ek olarak, öznel zamanın geçişi bir anket aracılığıyla incelenmiştir.

Bulgular: Mann Whitney U testi uygulanmıştır. Bağımlı değişkenler olarak öznel eşitlik noktası, Weber oranı ve ayrım eşiği kullanılmıştır. Genç ve yaşlı katılımcılar benzer süre ayrıştırma performansları sergilemişlerdir ($p \geq 0,05$). Bununla birlikte, katılımcıların sözlü ifadeleri değerlendirildiğinde; yaşlı bireyler gençlere göre genellikle zamanın daha hızlı geçtiğini ve önümüzdeki bir kaç saatin daha yavaş geçeceğini beklediklerini belirtmişlerdir ($p \leq 0,05$).

Sonuç: Bu çalışmada bilişsel taleplerin görev karmaşıklığı azaltılarak en aza indirildiği zaman, saniye üstü aralıktaki zaman algısının yaşlanma ile korunduğu gösterilmiştir.

Anahtar sözcükler: Yaşlanma; Zaman algısı

INTRODUCTION

Interval timing requires cognitive resources such as attention, perception, and encoding of incoming temporal information; long-term memory for storage and retrieval; and comparisons with the reference temporal durations in working memory. These functions deteriorate with aging (1). Changes in time perception are reported in healthy aging (2,3) as in several other neuropsychiatric disorders such as Parkinson's Disease (3). However, the extent to which these changes are attributable exclusively to time perception is debated because of the confounding factors introduced by the underlying cognitive processes. There is a vast literature on time perception models which address relevant issues regarding time perception differences in older adults. Although these are beyond the scope of our study, curious readers may find important theoretical information in (3).

A meta-analysis conducted by Block et al. (2) demonstrated that young and old groups exhibit two main differences: older adult's time judgements are less accurate and less precise (4). Studies based on a clock-speed hypothesis indicated that slowing down the internal clock of elderly causes age-related changes in time perception (5,6).

Conversely, the role of cognitive functions in the time perception of aging adults are not negligible (7,8). The authors in this camp state that inaccuracy in the time judgments of old individuals stem from the reduction in cognitive functions such as working memory and attention. Various studies reported that there are high correlations between cognitive abilities and temporal judgments.

In a recent temporal bisection study, a lower sensitivity to time in older participants than in younger participants is reported; and this reduction in temporal sensitivity was explained by the deterioration of attention with aging (4).

Recently, Droit-Volet et al. (9) demonstrated that cognitive demands alter as a function of the preferred temporal task. No aging effects in temporal performance in time bisection tasks were observed in various studies (7,10,11), whereas a difference emerged in other tasks. Conversely, if the complexity of the task increased, demanding more cognitive processing, the aging effects became more prominent (2,7,8). Moreover, an age-related decline in attentional resources may explain some of these timing deficits (8). Although younger participants are flexible and can allocate attention to the characteristics of a task, the decline of cognitive functions may be one reason why older adults focus more on some other unrelated stimuli during the task (7,8).

As indicated above, stimuli range is another crucial factor. For example, when older participants were supported by the appropriate feedback, they performed comparably to young individuals at short intervals (10). However, in studies using long intervals, older individuals exhibited a poorer performance compared to younger individuals.

Based on the above-mentioned factors, this study is designed to minimize the attentional-, motor-, and memory-related demands of the task so that the pure differences in time perception between two age groups, young and old adults, can be measured.

Previously, Akdoğan & Balcı (12) investigated the effects of payoff manipulations on temporal bisection performance, but to the best of our knowledge, this is the first study to investigate time perception performances of Turkish adults in a time bisection task in terms of aging effects.

The main factors affecting the design:

1) The temporal task demanding the least cognitive capacities is the time bisection task (9). To minimize attentional load, the time bisection task was preferred.

2) During the task, an experimenter was in charge of pressing the appropriate button according to the verbal response of the old participants. This is preferred to minimize: a. the performance effects derived from the stress responses of old participants

who are unfamiliar with technology, b. contribution of age-related motor deficits (13).

3) Chronometric counting derived bias is a critical issue, particularly in developmental perspective in which differences in counting ability arises (11). The best method of preventing chronometric counting is to give instructions to not count (14). Thus, before the onset of the session, each participant was told that he/she must not count.

4) A control experiment was designed to determine the visual acuity threshold of the participants and to ensure that timing performances were not affected by the visual deficiencies.

MATERIALS AND METHOD

Participants

A total of 66 volunteers participated in the study, including 33 young adults (mean age ± SD: 25.31 ± 3.5 years (range 18–35), 13 F, 20 M) and 33 old adults (mean age ± SD: 67.63 ± 4.87 years (range 60–78), 16 F, 17 M). For further analysis, the participants were categorized into four age groups intuitively: Young (18–25 years), middle-young (26–35 years), young-old (60–70 years), and old-old (71–80 years), similar to (11). The participants were recruited via distributed fliers, social media and with the help of our circle of acquaintances. The participants' demographic information is presented in Table 1. This study was approved by the METU Ethics Committee. All of the participants read and signed informed consent according to the principles of the Declaration of Helsinki. All participants had normal or corrected-to-normal vision and reported having no history of a neuropsychological/psychiatric disorder or alcoholism and no use of medication affecting the central nervous system.

Table 1. Demographic information of the participants.

	Old	Young
Age (Mean ± SD)	67.63 ± 4.87	25.31 ± 3.50
Gender	F = 16 M = 17	F = 13 M = 20
Years of Education (Mean ± SD)	12.38 ± 4.80	18.47 ± 2.85
SMMSE (Mean ± SD)	26.34 ± 0.46	-
GDS (Mean ± SD)	5.28 ± 0.84	-

Data Collection

1.Procedure

All participants were tested individually in a quiet room, either in their homes or on a university campus. They were seated in front of a PC (ASUS K55VJ–SX077D, Gpu: NVIDIA® GeForce® GT 635M). The experimental stimuli were presented via SuperLab 4.0 software (15). The responses were recorded with a standard Qwerty keyboard.

2. Time Bisection Task

A red circle (6 cm diameter) was displayed in the center of the computer screen on a white background. The short and long anchor durations were 1.25 and 2.5 s, respectively, and the probe durations were 1.25, 1.458, 1.667, 1.875, 2.083, 2.292, and 2.5 s. The experimenter pressed the appropriate button according to the participant's verbal response indicating a binary time judgement (short or long) related to the appearance of the red circle. A 500 ms feedback was presented after each short and long anchor duration. Feedback was provided for correct and incorrect responses in the form of tick and cross pictures, respectively.

A session included three phases: Pre-training, training, and testing. In the pre-training phase, the two anchor durations were presented in sequence: Three short and three long anchor durations. The experimenter introduced the durations by saying "This circle appears on the screen for a short/long time.", and no response was expected from the

participant. In the training phase, the participants learned to respond by pressing "S" for short and "L" for long durations. Two blocks of 10 trials, each including five short and five long stimuli, were introduced. Appropriate feedback was given after each response. The inter-trial interval varied between 0.5 and 2 s (4). If more than 70% of the participant's responses were correct in the second phase, the testing phase was presented (4). The same procedure used for training was used in the testing phase with the addition of probe durations, but feedback was given only for the shortest and longest durations. The testing phase was composed of 10 blocks of seven trials each (70 testing trials): There was one trial for each S and L anchor and the five intermediate durations. The presentation of these trials was randomized in each block. The task design is presented in Figure 1.

3. Visual Acuity Task

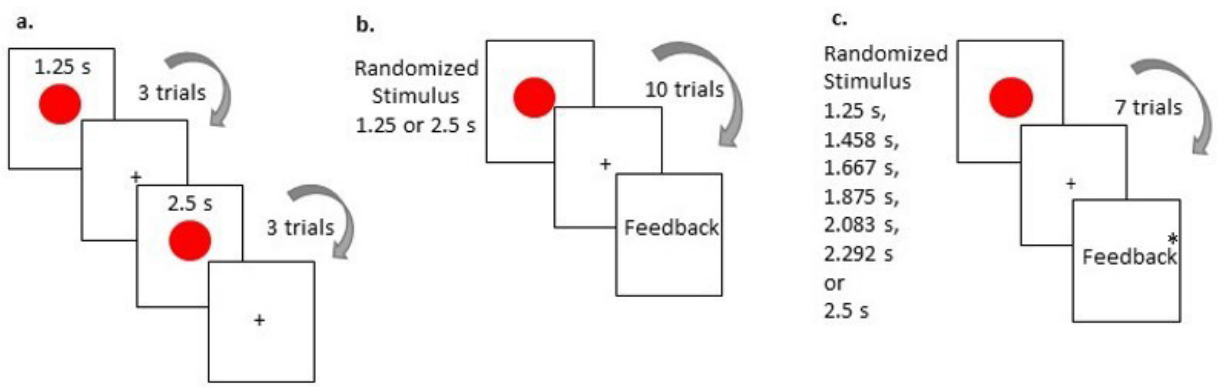
The red circle used in the time bisection experiment was modified by adding various levels of transparency. In total, 29 stimuli were created in MATLAB with varying transparency levels (0.004 (mostly transparent), 0.008, 0.012, …, 0.40, 0.70, 1 (opaque)). Each stimulus was displayed for 1.25 s and then the participant was asked to decide whether they saw a colorful circle. If the answer was "yes," they were told to press "+"; otherwise, they were told to press "-"; no feedback was given. Each participant completed five blocks of 29 randomized trials.

4. Questionnaires

The participants were asked to complete a questionnaire entitled, "Speed of Time" (16). The items given below were rated with a five-point scale.

1. How fast does time usually pass for you?
2. How fast do you expect the next hour to pass?
3. How fast did the previous week pass for you?
4. How fast did the previous month pass for you?
5. How fast did the previous year pass for you?
6. How fast did the previous 10 years pass for you?

Figure 1. Time bisection task design. a. Pre-training phase, b. Training phase: 2 blocks with 10 trials, c. Testing phase: 10 blocks with 7 trials. *Feedbacks in the testing phase were given only for the anchor durations (1.25 and 2.5 s).



To determine whether the older participants were cognitively healthy, the Standardized Mini Mental State Examination (SMMSE) (17) and Geriatric Depression Scale (18) were administered. The cut-off scores were 25 and 11, respectively. All participants fulfilled these criteria, as indicated in Table 1.

5. Measurements

The bisection point (BP) is defined as the stimulus duration which is evaluated as short or long with equal probability. By investigating the curve-fitted data of each participant, the signal duration corresponding to 50% of the long responses (i.e., p(long) = 0.5) was calculated and reported as the BP. The difference limen (DL) is a measure of variability calculated by subtracting the stimulus duration corresponding to 25% of responses evaluated as "long" from the stimulus duration at which 75% of the responses were evaluated as "long" and then divided by 2. A larger DL corresponds to a lower sensitivity and vice versa. The Weber ratio (WR) is defined as the relative temporal sensitivity and is calculated by dividing the DL by the BP. A lower WR is reflective of greater sensitivity to time.

RESULTS

1. Time Bisection

The probability of the long responses is plotted against the stimulus duration as presented in Figure 2. For further analysis, the BP, WR, and DL were calculated by fitting a logarithmic function to the psychophysical functions from individuals in MATLAB via psignifit 4 software (19). One young participant (insufficient fit) and one old participant (failure to reach the 70% success criterion in the second training block) were excluded from the study.

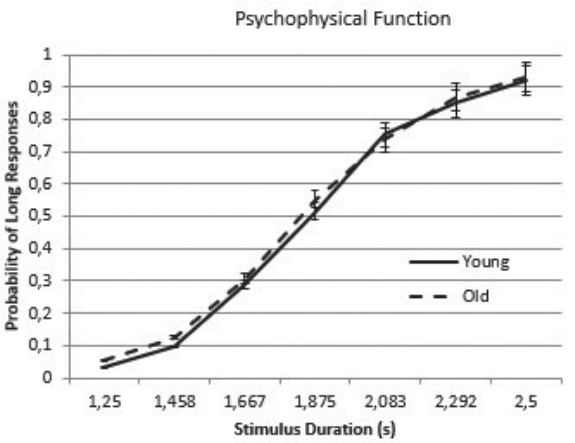
Outliers were checked by using z-scores with a threshold set at 3.29 (20). There was no z-score greater than 3.29, so no data was excluded. Data was non-normally distributed, the Mann-Whitney U test indicated that the BP of the young participants (Mdn = 1.885) did not differ significantly from that of the old subjects (Mdn = 1.873, U = 553, z = 0.551, ns). Additionally, the WR of the young participants (Mdn = 0.098) did not differ significantly from that of the old subjects (Mdn = 0.0984, U = 524, z = 0.161, ns). Similarly, the DL of the young participants (Mdn = 0.196) did not differ significantly from that of the old subjects (Mdn = 0.183, U = 534.5, z = 0.302, ns). Table 2 demonstrates the outcomes of the time bisection experiment.

Table 2. Time bisection experiment outcomes (median ± SD).

	Old	Young
BP	1.867 ± 0.032	1.881 ± 0.020
WR	0.107 ± 0.008	0.109 ± 0.008
DL	0.198 ± 0.014	0.206 ± 0.016

BP: Bisection Point; WR: Weber Ratio; DL: Difference Limen

Figure 2. Proportion of long responses versus stimulus duration.

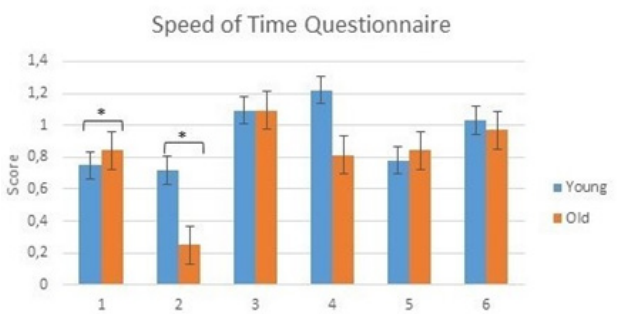


None of the variables exhibited significant effects of aging through four age categories. Mann-Whitney U test showed that years of education of young participants (M=18.47, SD=0.504) were significantly higher than old ones (M=12.38, SD=0.84), U=60.5, z= -6.073 p≤.001. This might have affected time bisection performance but, the correlation analyses indicated that there was no relationship between education levels and BP, WR and DL. Also, a regression analysis was conducted to investigate the effect of age and education together on BP, WR, and DL which indicated insignificant relationship among them.

2. Visual Acuity Task

Psychometric functions were calculated for each subject, and a logarithmic function was fitted. The probability of saying yes was plotted against the stimulus range. BP was calculated on curve-fitted data, and this value was defined as the visual acuity threshold. Since the data were non-normally distributed, the Mann-Whitney U test was conducted. The visual acuity threshold of the young participants (Mdn = 0.0256) did not differ significantly from that of the old participants (Mdn = 0.0297, U = 397, z = −1.544, ns). This was also replicated in the four age categories. There was no age effect on visual acuity threshold, which indicates that the young and old participants' vision did not differ.

Figure 3. Mean ratings of the young and old adults on items 1–6 of the speed of time questionnaire. The scores represent time passing: Very slowly [−2], slowly [−1], neither fast nor slow [0], fast [1], and very fast [2].



3. The Speed of Time Questionnaire

An independent samples median test showed that there was a significant trend of higher scores in item 2 for young subjects (Mdn = 1) than for old subjects (Mdn = 0, $\chi 2 = 7.570$, $p \leq 0.01$).

When the items were compared according to the four age groups, the independent samples median test demonstrated a significant difference among young (Mdn = 1), middle-young (Mdn = 1), young-old (Mdn = 1), and old-old (Mdn = 1) age groups for item 1 ($\chi 2 = 10.353$, $p \leq 0.05$) (Bonferroni corrected). Item 2 was also rated as significantly different among the young (Mdn = 1), middle-young (Mdn = 1), young-old (Mdn = 0), and old-old (Mdn = 0) age groups ($\chi 2 = 9.339$, $p \leq 0.05$) (Bonferroni corrected).

The factorability of six items was examined using Principal Component Analysis and a rotation method of Varimax with Kaiser Normalization. The sampling adequacy was verified with the Kaiser-Meyer-Olkin measure, KMO=.646. According to Bartlett's test of sphericity $\chi 2(15) = 60.499$, p≤.001, correlations between variables were sufficiently large for PCA. Overall analyses yielded two factors: Item 1 and 2 constituted a factor related to present time perception. The other four items regarding past time information formed a second factor. Two components had eigenvalues over than Kaiser's criterion of 1 and they jointly explained 56.05% of the variance. Furthermore, the reliability of the questionnaire is verified (the value of Cronbach's alpha = 0.668).

DISCUSSION

Although a decline is reported in various studies (5,8) in sensitivity to time in elderly, such a difference in the time bisection task was not observed in this study. The BP, WR, and DL were similar between the two age groups. In this study, the BP finding in previous studies (7,8,10,11) is replicated.

The strict control of our task design in terms of

cognitive demands might be a reason. The possible effects of cognitive decline observed in aging were minimized by the choice of a less complex task in terms of how time is reported as well as how motor responses are collected. Additionally, an experimenter recorded the old participants' responses to eliminate the likely effects of age-related motor deficits on task performance.

The similar timing performance of the two age groups may stem from compensation strategies. Previously, it was demonstrated that healthy elderly frequently realize their cognitive deficits, and a significant correlation between timing performance and the awareness of susceptibility to time distortion is reported (21). If the participants were more aware of their deficit, their temporal judgments were more accurate and precise. Moreover, the authors clarified that the older participants used compensation to improve their performance such that more attentional resources were allocated to the temporal task. This outcome can be interpreted as follows: The elderly in this study might have used compensation strategies. On another front, it was shown that education levels of the young and old participants differ. Although it might be a candidate factor affecting temporal judgements, correlation and regression analyses showed that there was no relationship between education levels and BP, WR and DL. Hence an interference due to education levels cannot be a contributing factor to the results.

There was a difference in the self-rated reports of time perception between the young and old participants. For item 1, which measures how fast time passes for the individual, the older participants' scores were higher than their younger counterparts. This might reveal a folk theory about aging and time perception. Older adults are influenced by a general belief that "time appears to pass more quickly as people grow older." The ratings of item 2 reveal that older participants expect the next hour to pass slower. This expectation might be a result of the older participants believing that the next hour, in which the experiment would be conducted, would be challenging for them. Our results did not support those obtained by Wittmann and Lehnhoff (16), who found a significant age-related effect only in item 6 of this questionnaire.

Finally, the effects of the environmental setting must be addressed. There is a discrepancy between the experimental environment and real life, which leads to differences between attentional demands. The internal clock of older adults shows a larger discrepancy between the lab environment and daily life since they are more susceptible to distractions than younger adults (5). Older adults' internal clocks may run faster during the experiment than in daily life.

CONCLUSION

Through this study, it is demonstrated that the perception of time in the supra-second range is preserved with aging when cognitive demands are minimized by reducing task complexity. Only psychometric measurements were used in this study; additional neuropsychology test batteries are imperative for detailed assessment of the cognitive states of the participants. Additional research is necessary to unveil the time perception and interval timing behavior of older participants at other time interval scales.

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CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

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RESEARCH

EFFECT OF PLANNED TRAINING PROVIDED TO CARE STAFF IN NURSING HOMES ON THEIR ATTITUDES TOWARD THE ELDERLY

Abstract

Introduction: The aim of this study was to determine the effect of planned training provided to care staff in nursing homes on their attitudes toward the elderly.

Materials and Method: The study was conducted between July and September 2018 using the one-group, pre-test–post-test trial model and quasi-experimental study design. The study population comprised 45 care staff members in only one nursing home, and the study sample comprised 38 care staff members. Data were collected through the Information Form, Attitude toward Old People Scale, and Ageism Attitude Scale. Necessary ethical approval and permissions for the study were obtained. Care staff members were provided planned training 3 days per week for a month, and the effectiveness of the training was evaluated pre- and post-test.

Results: There was a statistically significant difference between the pre- and post-test mean scores of the Attitude toward Old People Scale and Ageism Attitude Scale (Restricting Life of the Elderly, and Positive Ageism and Negative Ageism subscales) ($p < 0.05$).

Conclusion: Planned training provided to care staff positively affected their attitudes toward the elderly and ageism. These results indicate that establishing a planned training program for care staff in a nursing home is important in terms of the quality of care they provide.

Keywords: Nursing home; Nursing staff; Education; Aged

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ARAŞTIRMA

HUZUREVİNDE ÇALIŞAN BAKIM PERSONELLERİNE VERİLEN PLANLI EĞİTİMİN YAŞLILARA KARŞI TUTUMLARINA ETKİSİ

Öz

Giriş: Bu çalışma huzurevinde çalışan bakım personellerine verilen planlı eğitimin yaşlılara karşı tutumlarına etkisini belirlemek amacıyla yapılmıştır.

Gereç ve Yöntem: Araştırma tek grup ön test-son test deneme modeli ile yarı deneysel olarak sadece bir Huzurevi'nde çalışan bakım personelleri üzerinde, Temmuz-Eylül 2018 tarihleri arasında yürütülmüştür. Araştırmanın evrenini huzurevinde çalışan N=45 bakım personeli, örneklemi ise 38 bakım personeli oluşturmuştur. Araştırmanın verileri; Bilgi Formu, Yaşlılara Karşı Tutum Ölçeği ve Yaşlı Ayrımcılığı Tutum Ölçeği ile toplanmıştır. Araştırma için gerekli etik onay ve izinler alınmıştır. Bakım personellerine 1 ay boyunca haftada 3 gün planlı eğitim yapılmış ve eğitimin etkinliği ön test-son test ile belirlenmiştir.

Bulgular: Araştırmada bakım personellerinin Yaşlılara Karşı Tutum Ölçeği ve Yaşlı Ayrımcılığı Tutum Ölçeği ile Yaşlının Yaşamını Sınırlama, Yaşlıya Yönelik Olumlu Ayrımcılık ve Yaşlıya Yönelik Olumsuz Ayrımcılık alt boyutlarının ön test son test puan ortalamaları arasında istatistiksel olarak anlamlı bir farklılık olduğu bulunmuştur ($p<0.05$).

Sonuç: Araştırmada bakım personellerine verilen planlı eğitimin, bakım personellerinin yaşlılara karşı tutumlarını ve yaşlı ayrımcılığı tutumlarını olumlu yönde etkilediği belirlenmiştir. Bu sonuçlar doğrultusunda; huzurevinde çalışan bakım personellerine planlı eğitimlerin yapılması verecekleri bakımın kalitesi açısından önemli olacaktır.

Anahtar sözcükler: Huzurevi; Bakım personeli; Eğitim; Yaşlı

INTRODUCTION

IThe elderly population has been increasing in the world as well as in Turkey (1). According to the Turkish Statistical Institute data, the elderly population in Turkey has increased by 17% in the last five years from 5.891.694 in 2013 to 6.895.385 in 2017 (2). These data indicate that elderly health and healthcare services for the elderly are an important issue in Turkey (1,3). As the number of elderly people and diseases specific to old age increase, it is becoming increasingly difficult for family members to provide care for the elderly due to changes in social structure in recent years (4,5). Therefore, care institutions are increasingly relied upon under present-day circumstances to meet the needs of elderly people with various health problems and those who require care (4). Elderly people living in nursing homes are cared for by the care staff members who assume many responsibilities while caring for the elderly (6). Typically, care staff members around the world undergo basic training in health, home management, human relations, and social services and receive in-service training and undergo supervision regularly. Since this is a newly developing field in Turkey, the training and background of the care staff are not at the desired levels (3,7). Therefore, the approach of care staff toward the elderly may be variable. Attitudes of care staff toward the elderly are very important for the effectiveness of care they provide (8). Studies have shown that the attitudes of care staff toward the elderly also affect their care behaviors (9,10). Therefore, drawing attention to the issue of aging among those providing care to the elderly and raising their awareness on this issue are important in terms of developing their positive attitude toward the elderly (11,12). To this end, it is important to increase the awareness and capacity of care staff by providing planned training (13,14). Indeed, the lack of information among care staff affects their attitudes toward the elderly (15). Therefore, the present study was conducted to determine the effect of planned training provided to care staff on their attitudes toward the elderly.

Study Hypothesis

H0: Planned training provided to care staff in a nursing home does not affect their attitudes toward the elderly.

H1: Planned training provided to care staff in a nursing home positively affects their attitudes toward the elderly and ageism.

MATERIALS AND METHODS

The study was conducted between July and September 2018 using the one-group, pre-test–post-test trial model and quasi-experimental study design. Care staff are the people who support elderly care in nursing homes but they are not health care professionals; they are trained about elderly care by Public Education Centers for 560 hours. The study population comprised 45 care staff members in only one nursing home, and the study sample comprised 38 care staff members who were actively working during the study period, who consented to communication and collaboration, who volunteered to participate in the study, and who regularly attended the training activities. Prior to the study, written permission, ethics approval, and written and verbal consents were obtained from the care staff.

Data Collection Tools

Data were collected using the Information Form, Attitude Toward Old People Scale, and Ageism Attitude Scale.

Information Form: This form was prepared by the researchers according to the literature and included nine questions regarding sociodemographic characteristics of the care staff (4,10,16).

Attitude toward Old People Scale: The scale was developed by Nathan Kogan to measure attitudes of individuals toward the elderly. The scale comprises 34 items, with 17 of them being negatively worded and 17 being positively worded.

Questions with an odd number are negatively worded, while questions with an even number are positively worded. All points are summed up to determine the total score (17). The version of the scale used in this study was a 26-item form adapted to the Turkish society. For items from 1 to 26, the total score that can be obtained on the scale is a minimum of 26 and a maximum of 156. A higher total score indicates a positive attitude toward the elderly (18).

Ageism Attitude Scale: The scale developed by Vefikuluçay and Terzioğlu comprises and 23 items across 3 subscales, including the Restricting Life of the Elderly, Positive Ageism, and Negative Ageism subscales. It is a 5-point Likert scale, with the multiple choices including "Strongly disagree," "Disagree," "Neither agree nor disagree," "Agree," and "Strongly agree" for each item pertaining to the elderly. The highest attainable score is "115," while the lowest possible score is "23" (19).

Data Collection

Data were collected through face-to-face interviews conducted by the researchers. Pre- and post-test data collection forms were administered to the care staff in the conference room of the nursing home for approximately 15–20 minutes.

Training Program

Training activities for the care staff were conducted 3 days per week (Monday, Wednesday, and Friday) for a month (20,21). The topics of the training were planned according to the literature and were grouped under 10 headings (13,22). The training activities were conducted in a multipurpose hall in the nursing home for a total of 12 hours (1 hour per day; 3:00–4:00 PM). The training activities were implemented using power point presentations and interactive training methods.

Data Analysis

Data were analyzed using SPSS 20.0 package software. Descriptive statistics, independent samples t-test, variance analysis, correlation test, and paired t-test were used to analyze data. The level of statistical significance was set at $p = 0.05$.

RESULTS

In this section the results of the present study conducted to determine the effect of planned training provided to care staff in only one nursing home on their attitudes toward the elderly. Mean age of the care staff was 41.00 ± 7.89 years, and mean work experience were 8.26 ± 5.58. Overall, 71.1% of the care staff members were female, 86.8% were married, 50% were high school graduates, 57.9% had lived the longest in cities, 65.8% had a middle income, 65.8% lived in a nuclear family, and 76.3% lived with the elderly (Table 1).

Age of the care staff was significantly correlated to the scores of the Positive Ageism and Negative Ageism subscales of the Ageism Attitude Scale ($r=-0.398$; $p<0.05$) (Table 2). Moreover, sex of the care staff was significantly correlated to the score of the Restricting Life of the Elderly subscale of the Ageism Attitude Scale ($t=2.491$; $p< 0.05$) (Table 2).

Moreover, the pre- and post-test scores of the Attitudes Toward Old People Scale and the Restricting Life of the Elderly, Positive Ageism, and Negative Ageism subscales of the Ageism Attitude Scale were significantly different ($p < 0.05$) (Table 3).

DISCUSSION

The attitudes of care staff members—who are important in today's society—toward the elderly are important for the quality of care they provide (9). The findings of this study indicated that the age of the care staff affected their attitude toward ageism. As the age of the care staff increases, their positive attitudes toward ageism decrease. In addition, sex of the care staff affected their attitudes, as determined by the Restricting Life

Table 1. Sociodemographic characteristics of the care staff participating in the training.

Characteristics		**Mean ± SD (Range)**	
Age (years)		41.00 ± 7.89 (23–56)	
Work experience		8.26 ± 5.58 (2–21)	
		N	%
Sex	Female	27	71.1
	Male	11	28.9
Marital status	Married	33	86.8
	Single	5	13.2
Educational background	Primary school	4	10.5
	Secondary school	10	26.3
	High school	19	50.0
	Undergraduate	2	5.3
	Graduate	3	7.9
Longest residence	Village	12	31.6
	District	4	10.5
	City	22	57.9
Income level	Low	2	5.3
	Middle	25	65.8
	High	11	28.9
Family type	Nuclear	25	65.8
	Extended	13	34.2
Living with the elderly	Yes	29	76.3
		9	23.7
Total		**38**	**100.0**

B, Regression coefficient; SE, Standard error; β, Beta value; CI, Confidence interval; AChE. Acetylcholinesterase; 25(OH)D, 25-hydroxyvitamin D
* P value < 0.05, ** P value < 0.01

of the Elderly subscale of the Ageism Attitude Scale; female members of the care staff exhibited a more positive attitude. In addition, marital status, educational background, the place of the longest residence, income level, type of family, work experience, and age of the care staff did not affect their ageism attitude. Pekçetin has found that sociodemographic characteristics of the care staff do not affect their attitudes toward aging (16). Meanwhile, Bulut and Çilingir have described that educational background of surgical nurses affects their attitude toward aging (10). In our study, the association of age and sex of the care staff with their attitudes toward ageism was attributed to the facts that as the age of the care staff increases, their ability to cope with the elderly decreases and that care is considered a duty of women in our social structure. In a systematic review, Neville and Dickie have reported that the attitude toward the elderly is affected by age, sex, education, culture, institutional characteristics, and personality of the employee (9). In contrast, Ayaz Alkaya et al. (11) have stated that living at home with elderly people and providing care to elderly family members affect the attitudes toward the elderly. In addition, Ucun et al. (23) have stated that sociodemographic characteristics of young people do not affect their attitudes toward older individuals. Our findings indicate that the attitudes of the care staff towards the elderly was affected according to their socio-demographic variables - specifically age and sex.

In this study, there was statistically significant difference between pre- and post-test mean scores of the Attitudes toward Old People Scale and Ageism Attitude Scale. Moreover, the attitudes of the care staff toward the elderly and ageism, which were moderate pre-test, positively changed with the planned training. Similarly, Lee et al. (24) have stated that attitudes toward the elderly can positively change with education. In a single-group, pre-test–post-test study conducted by Baumbusch et al. (21) a 4-week training program for nursing students positively affected their knowledge of and attitudes toward the elderly. Rodgers and Gilmour have reported that the training provided to nursing students regarding the elderly showed a positive effect on their attitudes toward older people (25). In addition, in a study of care staff in nursing homes, Board et al. (20) have stated that the training program on dementia positively affected knowledge and attitudes of the participants. The present study showed the attitudes and knowledge of included care staff changed positively, which is consistent with the literature.

Nonetheless, this study has two major limitations. First, the results can only be generalized to this particular group since the research was conducted including care staff in a single nursing home. Second, since there was only one nursing home in the province where the study was conducted and the number of employees was low, the single-group, pre-test–post-test trial model was used, and no control group was included.

CONCLUSION AND RECOMMENDATIONS

In this study, planned training provided to care staff in a nursing home positively affected their attitudes toward the elderly and ageism. Our results indicate that supporting the care staff members who are becoming increasingly important as they provide care to the growing population of the elderly by establishing training programs on different aspects at regular intervals is imperative in terms of the quality of care they provide. Nonetheless, similar studies should be conducted including large cohorts of care staff members working in different nursing homes and institutions as well as a control groups using post-test follow-up models to monitor changes in attitudes.

Table 2. Mean Attitudes toward Old People and Ageism Scale Scores by Participant Sociodemographic Characteristics

Characteristics		Attitude Toward Old People Scale	Ageism Attitude Scale	Ageism Attitude Subscales		
				Restricting Life of the Elderly	Positive Ageism	Negative Ageism
Age (years)		41.00 ± 7.89	41.00 ± 7.89	41.00 ± 7.89	41.00 ± 7.89	41.00 ± 7.89
Test/P		r = 0.108/p = 0.517	r = −0.398*/p = 0.013	r = −0.134/p = 0.421	r = −0.393*/p = 0.015	r = −0.323*/p = 0.048
Work experience		8.26 ± 5.58	8.26 ± 5.58	8.26 ± 5.58	8.26 ± 5.58	8.26 ± 5.58
Test/P		r = −0.056/p = 0.739	r = −0.195/p = 0.240	r = −0.158/p = 0.343	r = −0.153/p = 0.358	r = −0.240/p = 0.147
Sex	Female	78.48 ± 10.23	17.56 ± 3.34	26.85 ± 4.84	11.56 ± 1.89	57.41 ± 7.75
	Male	77.00 ± 9.24	15.45 ± 1.81	28.00 ± 5.37	10.36 ± 1.96	56.27 ± 7.82
Test/P		t = 0.416/p = 0.680	t =.408/p = 0.685	t = 2.491/p = 0.018	t = −0.643/p = 0.524	t = 1.745/p = 0.089
Marital status	Married	77.73 ± 10.38	16.67 ± 3.06	26.76 ± 5.03	11.12 ± 2.09	56.36 ± 7.92
	Single	80.20 ± 5.36	18.80 ± 3.11	30.00 ± 3.67	11.80 ± 0.45	61.80 ± 3.42
Test/P		t = −0.518/p =0.608	t = −1.500/p = 0.142	t = −1.450/p= 0.156	t = −1.381/p= 0.176	t = −0.716/p = 0.478
Educational background	Primary school	85.75 ± 7.27	16.75 ± 1.89	25.00 ± 3.56	10.25 ± 0.96	53.00 ± 2.94
	Secondary school	78.40 ± 9.90	16.90 ± 4.36	27.20 ± 5.09	11.20 ± 2.25	56.40 ± 8.67
	High school	74.63 ± 10.19	17.11 ± 2.96	26.84 ± 5.35	11.42 ± 2.14	57.47 ± 8.37
	Undergraduate	86.00 ± 1.41	18.50 ± 2.12	31.50 ± 0.71	11.50 ± 0.71	63.50 ± 2.12
	Graduate	83.00 ± 3.00	15.33 ± 0.58	29.33 ± 4.93	11.00 ± 1.73	58.00 ± 5.29
Test/P		F = 1.858/p = 0.141	F = 0.649/p = 0.632	F = 0.318/p = 0.864	F = 0.715/p = 0.588	F = 0.290/p = 0.882
The longest residential place	Village	78.75 ± 10.92	16.58 ± 3.26	27.67 ± 5.60	11.50 ± 2.11	57.75 ± 8.62
	District	73.50 ± 10.54	17.25 ± 4.79	26.25 ± 2.36	11.25 ± 2.50	56.50 ± 6.95
	City	78.50 ± 9.39	17.09 ± 2.84	27.09 ± 5.07	11.05 ± 1.86	56.82 ± 7.59
Test/P		F = 0.466/p = 0.631	F = 0.066/p = 0.936	F = 0.119/p = 0.888	F = 0.126/p = 0.882	F = 0.200/p = 0.819
Income level	Low	77.00 ± 14.14	17.50 ± 3.54	22.50 ± 12.02	10.50 ± 0.71	50.50 ± 16.26
	Middle	76.72 ± 10.99	16.56 ± 3.29	26.68 ± 4.94	11.16 ± 2.15	56.48 ± 8.02
	High	81.27 ± 5.76	17.73 ± 2.72	29.18 ± 2.89	11.45 ± 1.69	59.64 ± 4.54
Test/P		F = 0.819/p = 0.499	F = 1.454/p = 0.247	F = 0.558/p = 0.578	F = 2.025/p = 0.147	F = 0.215/p = 0.807
Family type	Nuclear	77.40 ± 10.30	17.36 ± 3.00	26.24 ± 4.88	11.28 ± 2.03	56.56 ± 7.64
	Extended	79.31 ± 9.19	16.15 ± 3.29	29.00 ± 4.74	11.08 ± 1.89	58.08 ± 7.96
Test/P		t = −0.561/p = 0.578	t = 0.572/p = 0.571	t = 1.139/p = 0.262	t = −1.668/p = 0.104	t = 0.299/p = 0.767
Living with the elderly	Yes	78.10 ± 8.93	16.62 ± 2.81	27.55 ± 4.72	11.03 ± 1.82	56.97 ± 7.32
	No	77.89 ± 13.04	18.00 ± 3.94	26.00 ± 5.79	11.78 ± 2.39	57.44 ± 9.22
Test/P		t = 0.056/p = 0.955	t = 0.161/p = 0.873	t = −1.168/p = 0.250	t = 0.817/p = 0.419	t = 0.993/p = 0.327

t = Independent samples t-test, F = Variance analysis, r = *. Correlation is significant at the 0.05 level* P value < 0.05, ** P value < 0.01

Table 3. Regression coefficients of multiple linear regression in the second step.

	Pre-test	Post-test	Test	P value
	Mean ± SD	Mean ± SD		
Attitudes Toward Old People Scale	78.05 ± 9.85	81.58 ± 9.34	t= −3.682	0.001
Restricting Life of the Elderly	16.95 ± 3.11	19.71 ± 2.79	t= −5.563	0.000
Positive Ageism	27.18 ± 4.95	30.92 ± 6.04	t= −6.859	0.000
Negative Ageism	11.21 ± 1.96	12.45 ± 2.02	t= −3.751	0.001
Ageism Attitude Scale	57.08 ± 7.68	61.34 ± 6.72	t= −6.179	0.000

t = paired t-test

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