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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Evaluation of Healthcare Associated Bloodstream Infections at a Tertiary Care Hospital Between 2011 and 2015: Epidemiology and Mortality Risk Factors

Üçüncü Basamak Bir Hastanede, 2011–2015 Yılları Arasındaki Sağlık Bakım İlişkili Kan Dolaşımı Enfeksiyonlarının Değerlendirilmesi; Epidemiyoloji ve Mortalite Risk Faktörleri

Aliye Baştuğ[1], Esragül Akıncı[1], Adalet Aypak[1], Dilek Kanyılmaz[2], Halide Aslaner[1], Ayşe But[1], Meltem Arzu Yetkin[1], Pınar Öngürü[1], Hürrem Bodur[1]

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ABSTRACT

Aim: *Bloodstream infections (BSIs) are an important cause of mortality in hospitals. Local surveillance data should be taken into account to overcome these challenging infections. The aim of this study is to determine the microbiological characteristics of BSIs and the risk factors for mortality.*

Material and Method: *Active prospective surveillance data based on patient and laboratory were evaluated from January 2011 to June 2015. The first episodes of primary BSIs of the patients were included to the study. CDC case definitions were used to define BSIs. The data were recorded included demographics, underlying conditions, invasive procedures, fever (>=38°C) or hypothermia (<36°C), causative isolates and antimicrobial resistance patterns, appropriate antimicrobial therapy within 3 days after the onset of infection and outcome on day 14 after infection onset.*

Results: *During the study period 373 patients with health care associated BSIs were identified. Acinetobacter spp. was the most common isolate (20.4%, n=76), followed by Coagulase negative Staphylocccus (CoNS) (19.3%, n=72), Candida spp. (17.2%, n=64) and Klebsiella spp. (11%, n=41), respectively. Multidrug resistance ratio was 98.7% for Acinetobacter spp. Methicillin resistance was found 66.7% of Staphylococcus aureus (S.aureus) and 79.2% of CoNS. Extended spectrum beta lactamases (ESBL) ratio for Klebsiella spp. was 65% (26/40) and 67.9% (19/28) for E.coli. The mortality rate of the patients in the first 14 days was 37.8% (n=141). Logistic regression analysis re-vealed that, BSIs due to the Acinetobacter spp. and Candida spp. had 2.35 and 2.48 times higher mortality rates, respectively. Inappropriate antimicrobial therapy, presence of hypothermia, steroid usage, dialysis and presence of two or more underlying conditions were other independent predictors for mortality.*

Conclusion: *It is important to perform active surveillance for BSIs which result in high mortality rates due to resistant isolates. Appropriate antimicrobial therapy is crucial since it has a significant impact to decrease mortality.*

Key words: *bloodstream infections; mortality predictors; epidemiology*

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ÖZET

Amaç: *Kan dolaşımı enfeksiyonları (KDE) hastanelerde mortalitenin önemli nedenlerindendir. Bu enfeksiyonları yönetebilmek için lokal surveyans verileri göz önünde bulundurulmalıdır. Bu çalışmanın amacı; kan dolaşımı enfeksiyonlarında mikrobiyolojik karakteristikleri ve mortalite risk faktörlerini belirlemektir.*

Materyal ve Metot: *Ocak 2011 ve Haziran 2015 yılları arası hasta ve laboratuvara dayalı aktif prospektif surveyans verileri değerlendirildi. Çalışmaya primer kan dolaşımı enfeksiyonu olan hastaların ilk epizodları dahil edildi. Kan dolaşımı enfeksiyonlarını tanımlamak için CDC tanı kriterleri kullanıldı. Kaydedilen veriler arasında; demografik veriler, altta yatan hastalıklar, invaziv işlemler, ateş (≥38°C) veya hipotermi (<36°C) varığı, etken izolatlar ve antimikrobiyal direnç paternleri, hastalığın başlangıcı sonrası ilk 3 gün içinde uygun antibiyotik kullanımı ile 14 gün içindeki mortalite yer almaktadır.*

Bulgular: *Çalışma süresince sağlık bakım ilişkili kan dolaşımı enfeksiyonu olan 373 hasta tanımlandı. Acinetobacter en sık saptanan izolat (%20,4, n=76) olup sonrasında sırasıyla Koagulaz negatif stafilokoklar (KNS) (%19,3, n=72), kandida suşları (%17,2, n=64) ve Klebsiella suşları (%11, n=41) saptandı. Acinetobacter suşları arasında çok ilaca direnç oranı %98,7 idi. Metisilin direnci S.aureus için %66,7 ve KNS için %79,2 bulundu. Genişlemiş spektrumlu beta laktamaz (ESBL) oranı Klebsiella suşlarında %65 (25/40) ve E.coli suşlarında %67,9 (19/28) idi. Hastalarda ilk 14 gün içindeki mortalite oranı %37,8 (n=141) idi. Lojistik regresyon analizi sonucunda; acinetobacter ve kandida izolatlarına bağlı kan dolaşımı enfeksiyonlarında sırasıyla 2,35 ve 2,48 kat daha fazla mortalite oranı saptandı. Uygun olmayan antibiyotik tedavisi, hipotermi varlığı, steroid kullanımı, diyaliz ve iki veya daha fazla altta yatan hastalık olması mortaliteyi gösteren diğer bağımsız faktörler olarak bulundu.*

Sonuç: *Dirençli izolatlara bağlı oluşan kan dolaşımı enfeksiyonları yüksek mortalite ile sonuçlandığından bu enfeksiyonlar için aktif surveyans yapılması önemlidir. Uygun antimikrobiyal tedavi mortaliteyi anlamlı olarak azalttığından oldukça önemlidir.*

Anahtar kelimeler: *kan dolaşımı enfeksiyonları; mortalite prediktörleri; epidemiyoloji*

Introduction

Bloodstream infections (BSIs) are one of the major health care associated infections in nosocomial setting and associated with significant morbidity and mortality. The causative microorganisms and resistance patterns of isolates vary in different setting and geographic regions[1,2]. In addition, increasing rate of the resistant microorganisms further complicate the problem and increase the mortality rate. For that reason, it is important to monitor the most frequent isolates and determine their resistance patterns since the early appropriate antimicrobial therapy is crucial to decrease the mortality. Therefore, the performance of active prospective surveillance and careful evaluation of the data regarding these infections are important[1–3].

The aim of this study was to evaluate the current epidemiology, isolate distribution and resistance patterns of causative microorganisms, in addition to the mortality risk factors and 14-day outcome after the onset of BSIs.

Material and Method

Patients and Hospital Settings

The present study was conducted in Ankara Numune Training and Research Hospital (ANTRH) in Turkey. Active prospective surveillance data based on patient and laboratory were evaluated from January 2011 to June 2015 in the 1140-bed tertiary care hospital. The data was gathered by the nurses working in infection control committee and infectious disease specialists. The criteria of Centers for Disease Control and Prevention (CDC) case definition was used to define BSIs. The first episode of primary BSIs of the patients ≥18 years from intensive care units and wards were included into the study. However, the patients with polymicrobial BSIs were excluded.

Data Collection

The data including; demographic characteristics, intensive care unit (ICU) stay, underlying conditions (e.g., diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease (COPD), invasive procedures (central venous catheter (CVC), mechanical ventilator (MV) etc.), support of total parenteral nutrition (TPN), fever (>=38°C) or hypothermia (<36°C), BSI type (CVC related or not), causative isolates and antimicrobial resistance patterns (Multidrug resistance (MDR), extended spectrum beta lactamases (ESBL), methicillin resistance), appropriate antimicrobial therapy within 3 days after the onset of infection, and 14-day outcome after the onset of infection were recorded.

Definitions

Definitions were provided in Table 1 based on the previous studies and guidelines[3–5].

Microbiological Tests

Isolate identification and antimicrobial susceptibility tests were performed using a VITEK automated system BioMerieux, Marcy I'Etoile, France). The Clinical and Laboratory Standards Institute (CLSI) criteria were used to determine the resistance or susceptibility

Table 1. *Definitions*

Laboratory-confirmed bloodstream infection (LCBI)[3]	Patients with at least has one of the following criteria; 1) Isolation of microorganisms from blood (such as E.coli, Klebsiella spp., Pseudomonas spp., S.aureus, Enterococcus spp., Candida spp, and others) for ≥1 positive culture that was not related to another infection of body sites 2) Patients with one of the following signs that was not related to another infection focus; fever (38°C), chills or hypotension and ≥2 positive different culture results for probable skin contaminant pathogens, such as Coagulase negative Staphylococcus (CoNs)
Laboratory-confirmed central venous catheter-associated bloodstream infections (CVC-BSI)[3]	Patients with a CVC had a recognized pathogen isolated from ≥1 percutaneous blood cultures after 48 h of central venous catheterization (unrelated with another infection). The patients should also have at least one of the following signs and symptoms: fever (38°C), chills, or hypotension. With the common skin commensals (e.g., diphtheroids, (CoNs)), the organisms had to have been cultured from ≥2 separate blood cultures
Multidrug resistant bacteria infection[4]	An infection due to a Gram-negative bacteria which has a resistance to ≥3 classes of antimicrobial agents
Appropriate antimicrobial therapy[5]	Administrated drug has in-vitro activity against the causative isolates according to antimicrobial susceptibility test results or administration of the drug within 72 h of the infection onset
14-day mortality	Death within 14 days of infection onset

to the antimicrobial agents[6]. ESBL production was determined and confirmed using a double-disc synergy test in line with CLSI guidelines[7].

Variables such as demographic characteristics, etiologic agents, antimicrobial resistance patterns of the isolates, inappropriate antimicrobial therapy and all other possible causes of mortality were identified. Survivors and non-survivors 14 days after the onset of BSI were compared to identify the predictors of the mortality. Continuous variables were described as median (min-max). Chi-square tests were used for categorical variables and Mann Whitney U tests were used for continued variables. The variables found to be significantly associated with mortality in the univariate analysis were included in Logistic regression analysis. p values <0.05 were considered statistically significant. Odds ratios and 95% confidence intervals (95% CI) were calculated. Statistical analysis was performed using SPSS 18.0.

Results

A total of 373 patients with health care associated BSIs were enrolled in the study, including 199 (53.4%) men. The median age was 62 (18–97 years). Of 373 patients, 252 were from intensive care units, 260 (69.7%) had one underlying condition, and 94 (25.2%) had ≥2 underlying condition. The predominant underlying condition was malignancy that was found in the 30.3% of the patients. Catheter related BSI was determined in 292 (78.5%) patients. Length of time to emergence of BSI was median 20 days (3–141 days). Fever (>38°C) was present in 63.5% of the patients (Table 2). Majority of the cultivated pathogens were

Table 2. *Basal characteristics of the patients*

Characteristics	Number of patients n (%)	Survivors (n=232) n (%)	Non-survivor (n=141) n (%)	P value
Age (median, min-max years)	62 (18–97)	56 (18–97)	68 (19–64)	**0.000**
Age >65 years	167 (44.8)	85 (36.6)	82 (58.2)	**0.000**
Gender (male)	199 (53.4)	132 (56.9)	67 (47.5)	>0.05
ICU stay at the time of infection	252 (67.6)	142 (61.2)	110 (78.0)	**0.001**
Central venous catheter related BSI	292 (78.3)	182 (78.8)	110 (78)	>0.05
Underlying conditions	260 (69.7)	148 (63.8)	112 (79.4)	**0.002**
Diabetes mellitus	45 (12.1)	21 (9.1)	24 (17)	**0.032**
COPD	24 (6.4)	11 (4.8)	13 (9.2)	>0.05
Renal failure	80 (21.4)	37 (15.9)	43 (30.5)	**0.001**
Hypertension	55 (14.7)	22 (9.5)	33 (23.4)	**0.000**
Congestive heart failure	15 (4.0)	6 (2.6)	9 (6.4)	>0.05
Serebrovascular disease	42 (11.3)	25 (10.8)	17 (12.1)	>0.05
≥2 underlying conditions	94 (25.2)	43 (18.5)	51 (36.2)	**0.000**
Malignancy	113 (30.3)	77 (33.5)	36 (25.5)	>0.05
Steroid usage	44 (11.8)	24 (17.0)	20 (8.6)	**0.020**
Mechanical ventilator	197 (52.8)	112 (48.3)	85 (60.3)	**0.025**
Dialysis	74 (19.8)	34 (14.7)	40 (28.4)	**0.002**
CVC	317 (85.0)	199 (85.8)	118 (83.7)	>0.05
TPN	113 (30.3)	64 (27.6)	49 (34.8)	>0.05
Fever (>38°C)	237 (63.5)	147 (63.4)	90 (63.8)	>0.05
Hypotermia (<36°C)	13 (3.5)	4 (1.7)	9 (6.4)	**0.022**
Presence of concurrent other infection	87 (23.3)	49 (21.1)	38 (27.0)	>0.05
Prior antibiotic therapy (>7 days, before the diagnosis of BSI)	229 (61.4)	127 (54.7)	102 (72.3)	**0.001**
Inappropriate antimicrobial therapy	158 (42.4)	71 (30.6)	87 (61.7)	**0.000**
Length of time to appropriate antimicrobial therapy (median, min-max days)	0 (0–3)	0 (0–3)	0 (0–3)	>0.05
Length of time to infection (median, min-max days)	20 (3–141)	20 (3–141)	20 (3–131)	>0.05
Central venous Catheterization time prior to infection (median, min-max days)	14 (0–64)	13 (0–64)	14.5 (2–49)	>0.05

*COPD: Chronic obstructive pulmonary disease, CVC: central venous catheter, TPN: total parenteral nutrition

Gram-negative bacteria (48.5%, n=181). *Acinetobacter* spp. was the most common isolates (20.4%, n=76), followed by *CoNS* (19.3%, n=72), *Candida* spp. (17.2%, n=64) and *Klebsiella* spp. (11%, n=41) (Table 3). When the causative isolates were compared between years 2014 and 2011, a significant decrease in the frequency of *Acinetobacter* spp. (15.6%, 15/96 vs 30.1%, 19/63, respectively p = 0.016) was detected. There was no other significant difference between years according to other pathogens.

Of total *Acinetobacter* spp. isolates, the ratio of multidrug resistance was 98.7%. Methicillin resistance was found in 66.7% of *S.aureus* and 79.2% of *CoNS*. ESBL ratio was 65% (26/40) for *Klebsiella* spp. and 67.9% (19/28) for *E.coli*. The frequency of resistance (%) to the main antimicrobial classes among the most prevalent isolates was summarized in Table 4. Empirical antibiotic therapy was applied in 76.9% of the patients. Inappropriate antimicrobial therapy was determined in 42.4% (n=158) of the patients, and it was significantly higher in fatal cases (61.7%). In addition it was defined as an independent predictor of mortality (p = 0.000, OR: 3.81, 95% CI: 2.2–6.3) (Table 5). The median length of time to appropriate antimicrobial therapy was 0 (0–3) day and there was no statistical difference between fatal and non-fatal groups. The mortality rate of the patients 14 days after BSIs was 37.8% (n=141). When the risk factors for mortality were evaluated in univariate analysis, older age (>65 years), ICU stay on the time of infection onset, presence of underlying condition, steroid usage, dialysis, hypothermia, inappropriate antimicrobial therapy, infections due to *Acinetobacter* spp. and *Candida* spp. were found as a significant risk factors for mortality (Table 2 and 3). Logistic regression analysis revealed that, BSIs due to the *Acinetobacter* spp. and *Candida* spp. had 2.35 and 2.48 times higher mortality rates, respectively. Inappropriate antimicrobial therapy, presence of hypothermia, steroid usage, dialysis and two or more underlying conditions were other independent predictors for mortality (Table 5).

Discussion

Bloodstream infections are the important causes of morbidity and mortality in nosocomial setting. Prevalence of BSIs, causative isolates and resistance patterns are different across the world[8]. For this reason, surveillance data should be evaluated carefully in order to start appropriate empirical antimicrobial therapy. There are different reports about the frequency of nosocomial infections. Although, bacteremia is reported as second frequent infections in ICU in some studies, it was reported as a most common health care associated infection in a multicenter study performed in our country[9–12]. It is an important health care problem, since it is frequent and many of the causative microorganisms have developed resistance to the most of the antimicrobials[13]. The present study focused on the identification of the epidemiologic characteristics and antimicrobial resistance patterns (ESBL, MDR etc.) of causative isolates and the predictors of mortality in patients with BSI. We determined the 14 day mortality rate as the main outcome measure and the mortality rate was detected as 37.8%. The median age was significantly higher in fatal cases (68 years) in univariate analysis which was not found as an independent predictor for mortality. Cevik et al. reported that, although statistically insignificant, patient with older age (≥70 years) had higher mortality rate[14] We evaluated the impact of underlying conditions on mortality, since the host defenses have an important role in patient outcome. The presence of ≥2 underlying conditions was detected as a significant risk factor for mortality (p = 0.018, OR: 1.98, 95% CI: 1.1–3.4) consistent with the literature[10]. Hypothermia, dialysis and steroid usage were also found as independent predictors of mortality.

When we evaluated causative microorganisms, we determined that Gram negative pathogens were the most common isolates different from the study of Inan et al., who reported *S.aureus* as a predominant pathogen in CVC related BSI in ICU[1]. The prevalent pathogen was *Acinetobacter* spp. (20.4%), followed by *CoNS* and *Candida* spp. in our study. *C.albicans* is the most common subspecies in *Candida* spp. consistent with the literature[15]. Higher mortality rates in Gram-negative BSIs were reported in previous studies than Gram-positive infections[16,17]. In the present study, similar with the literature, we demonstrated that infections with Gram-negative isolates had significantly higher whereas infections with Gram-positive isolates had significantly lower mortality rates. We thought that the low virulence of *CoNS* isolates may be the cause of lower mortality rates. BSIs with *Acinetobacter* spp. and C*andida* spp. were determined as independent predictors of mortality. In recent years, there has been a noticeable increase in health care associated infections caused by multidrug resistant pathogens[1,18]. Wide spectrum antibiotic usage (>7 days) prior to the onset of BSI was found in 61.4% of all patients, which may be one of the causes of high resistance rate in our study. It is known that, previous antibiotic usage leads to the selection of resistance pathogens[19].

Table 3. *Distribution of the causative isolates*

Microbial species	Total n (%) (n=373)	Survivors (n=232)	Non-Survivor (n=141)	P value
Gram-negative bacteria	181 (48.5)	101 (43.5)	80 (56.7)	**0.007**
Escherichia coli	29 (7.8)	20 (8.6)	9 (6.4)	>0.05
Klebsiella spp.	41 (11.0)	22 (9.5)	19 (13.5)	>0.05
Acinetobacter spp.	76 (20.4)	33 (14.2)	43 (30.5)	**0.000**
Other Gram negatives	35 (9.3)	25 (10.8)	9 (6.3)	-
Gram-positive bacteria	128 (34.3)	100 (43.1)	28 (19.9)	**0.000**
Coagulase negative staphylococci	72 (19.3)	60 (25.9)	12 (8.5)	**0.000**
Stapylococcus aureus	28 (7.5)	18 (7.7)	10 (7.0)	>0.05
Other Gram positives	28 (7.5)	22 (9.5)	6 (4.2)	-
Candida spp.	64 (17.2)	31 (13.4)	33 (23.4)	**0.007**
C.albicans	39 (10.5)	19 (8.2)	20 (14.2)	>0.05
C.nonalbicans	25 (6.7)	12 (5.2)	13 (9.2)	>0.05

Table 4. *Frequency of resistance (%) to the main antibiotics among the most prevalent causatives*

Species (n)	CAZ/ CRO	IMP/ MEM	AK/ GEN	CIP/ LEV	TZP	COLI	TIGE	ESBL	MDR	OXA	VAN/ TEIC
E.coli (28)	69	69	13.8	65.5	42.9	0	0	67.9	41.7	-	-
Klebsiella spp. (41)	68.3	94.7	61.8	66.7	71.8	0	0	65	60.5	-	-
Acinetobacter spp. (76)	98.7	94.7	61.8	96.1	97.4	2.6	50	-	98.7	-	-
CoNs (72)	-	-	-	-	-	-	-	-	-	79.2	0
S.aureus (28)	-	-	-	-	-	-	-	-	-	66.7	0

CAZ: ceftazidime, CRO: ceftriaxone, IMP: imipenem, MEM: meropenem, AK: Amikacin, GEN: gentamycin, CIP: ciprofloxacin, LEV: levofloxacin, TZP: piperacillin-tazobactam, COLI: colimycin, TIGE: tigecycline, ESBL: extended spectrum beta lactamases, MDR: multi-drug resistance, OXA: oxacillin, VAN: vancomycin, TEIC: teicoplanin

Table 5. *Independent predictors of mortality for patients with health care associated BSIs*

Independent variables	P value	OR	95% CI
Acinetobacter spp.	0.006	2.35	1.3–4.3
Candida spp.	0.005	2.48	1.3–4.7
Inappropriate antimicrobial therapy	0.000	3.81	2.2–6.3
≥2 underlying condition	0.018	1.98	1.1–3.4
Steroid usage	0.040	2.14	1.0–4.4
Hypothermia	0.011	5.34	1.4–19.5
Dialysis	0.011	2.26	1.2–4.2

Methicillin resistance was found 66.7% for *S.aureus* and 79.2% for *CoNS*. Inan et al. reported higher MRSA ratio (93.1%) previously[1]. ESBL comprised 67.9% of *E.coli* and 65% of *Klebsiella* spp., which were higher than the previous multicenter study in Turkey[18]. In addition, *Acinetobacter* spp. was usually resistant to the most of the antibiotics used empirically. In fact, multidrug resistance (MDR) rate of *Acinetobacter* spp. was 98.7% and carbapenem resistance was 94.7%, which is higher than the previous report of Yüce et al.[20]. We thought that invasive characteristics and resistance patterns of the *Acinetobacter* spp. had an impact on increased mortality rates. Since the MDR pattern reduces the count of effective antibiotic options, it is frequently related with poor outcome[21]. Appropriate antimicrobial therapy is crucial and is known to have a significant influence on decreasing the mortality of patients with BSI. In the present study, inappropriate antimicrobial therapy was determined as an independent predictor for mortality similar to previous studies[15,22]. In conclusion, we found that

infections due to the *Acinetobacter* spp. were predominant in patients with BSI. Because of the emergence of MDR isolates, it is becoming a clinical challenge to overcome these infections. Surveillance data should be evaluated carefully in nosocomial settings. The prevalent isolates and resistance patterns should be taken into account before starting empirical antimicrobial therapy, which is crucial to reduce mortality rate.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Radyoterapi Planında Kontrast Madde Kullanımının Doz Hesaplamasına Etkisi Var mıdır?

Is There Effect of Contrast Media Use on Dose Calculation in Radiotherapy Planning?

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ABSTRACT

Aim: *The aim of this study was to evaluate the effect of contrast-enhanced computed tomography (CT) scans on the radiation dose calculations for lung cancer treatment planning with intensity modulated radiotherapy (IMRT).*

Material and Method: *CT images used for radiotherapy (RT) planning of 10 patients with lung cancer were evaluated retrospectively. IMRT plans were used 5–7 coplanar beams according to tumor localization. The dose was 60 Gy. Contrast-enhanced and unenhanced doses of 50% (D50), 90% (D90) and 95% (D95) of planning target volume (PTV) were compared. Similarly, contrast-enhanced and unenhanced doses of spinal cord, which is one of critical normal structures, were compared. Contrast-enhanced and unenhanced percentages of volume of normal lung tissue, which is another of critical normal structures, received ≥20 Gy dose were also compared.*

Results: *There was no significant difference between contrast-enhanced and unenhanced PTV D95, D90 and D50 doses (p >0.05). Similarly, there was no significant difference between contrast-enhanced and unenhanced doses of spinal cord (p >0.05). There was also no significant difference between contrast-enhanced and unenhanced V20 percentages (p >0.05).*

Conclusion: *Our findings suggest that use of contrast agent has not significant effect on the dose calculation for lung cancer treatment planning with IMRT.*

Key words: *lung cancer; computed tomography; dose calculation; contrast agent; intensity modulated radiotherapy*

ÖZET

Amaç: *Bu çalışmanın amacı yoğunluk ayarlı radyoterapi (YART) ile akciğer kanseri tedavi planlaması için radyasyon doz hesaplamaları üzerine kontrastlı bilgisayarlı tomografi (BT) taramanın etkisini değerlendirmekti.*

Materyal ve Metot: *Akciğer kanserli 10 hastanın radyoterapi (RT) planlama için kullanılmış BT görüntüleri retrospektif olarak değerlendirildi. Tümörün yerleşimine göre 5, 6 ve 7 alan YART planlandı. Doz 60 Gy olarak belirlendi. YART plan değerlendirilmesinde PTV'nin %95'inin, dozun %95'ini alması hedeflendi. Planlanan hedef volümün (PTV) %50'sinin (D50), %90'ının (D90) ve %95'inin (D95) kontrastlı ve kontrastsız aldığı dozlar karşılaştırıldı. Benzer olarak kritik normal yapılardan olan spinal kordun kontrastlı ve kontrastsız dozları da karşılaştırıldı. Ayrıca kritik normal yapılardan olan normal akciğer dokusunun 20 Gy ve üzerinde doz alan volümünün (V20) kontrastlı ve kontrastsız yüzdeleri de karşılaştırıldı.*

Bulgular: *Kontrastlı ve kontrastsız PTV D95, D90 ve D50 arasında anlamlı fark saptanmadı (p >0,05). Benzer olarak kontrastlı ve kontrastsız spinal kord dozları arasında da anlamlı fark saptanmadı (p >0,05). Ayrıca kontrastlı ve kontrastsız V20 yüzdeleri arasında da anlamlı fark saptanmadı (p >0,05).*

Sonuç: *Bizim bulgularımız YART ile akciğer kanseri tedavi planlaması için doz hesaplaması üzerine kontrast madde kullanımının belirgin bir etkisinin olmadığını düşündürmektedir.*

Anahtar kelimeler: *akciğer kanseri; bilgisayarlı tomografi; doz hesaplaması; kontrast madde; yoğunluk ayarlı radyoterapi*

Giriş

Akciğer kanseri en sık görülen üçüncü kanser türüdür ve kanser nedenli ölümlerin en sık nedenidir[1]. Radyoterapi (RT) akciğer kanseri için önemli bir tedavi seçeneğidir[2].

İki boyutlu konvansiyonel RT ile tümörün yükseklik ve genişliğine göre RT tedavi sahaları belirlenirken, 3 boyutlu RT'de yükseklik ve genişliğe ilave olarak tümörün derinliği de göz önünde bulundurulur. Üç boyutlu konformal RT tümöre karşı olabilen en hassas ve yüksek, buna karşılık tümöre komşu normal dokularda en düşük dozun elde edilmesini sağlayan ve iki boyutlu RT tedavi planlamalarının eksikliklerini ortadan kaldıran, bilgisayar destekli bir RT teknolojisidir[3]. Konformal RT kullanımı ile istenilen şey; hedef hacimleri (tümör dokusu) yüksek doz ile tedavi ederken, kritik ve normal dokulara dozu (mümkün olduğunca) en aza indirmektedir[4]. Üç boyutlu konformal RT'de bilgisayarlı tomografi (BT)

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kesitlerinde hedef volüm rahatlıkla belirlenebileceği için, daha sınırlı alanlardan daha yüksek RT dozlarına çıkmak mümkün olabilmektedir[3]. En son teknolojik gelişmelerden biri olan yoğunluk ayarlı RT'de (YART) ise ışın demetinin doz yoğunluğu lifler ile ayarlanarak, uygun doz dağılımlarıyla tümöre maksimum, risk altındaki organlara minimum doz vermek olasıdır[3]. Bu da tedavi başarısını artırırken, RT ilişkili yan etkileri azaltmaktadır[4].

RT planlamasında BT ile simülasyon yapma imkanları mevcuttur. Aynı zamanda tedavi planlama için kullanılan BT sırasında otomatik enjektör yardımı ile eş zamanlı BT görüntüleri kontrastlı olarak elde edilebilmektedir. BT simülasyonu sırasında çekilen toraks BT'de özellikle mediastinal yapılar ve tümör ilişkisinin daha iyi ortaya konabilmesi için iyotlu intravenöz kontrast maddeler kullanılabilmektedir. Kontrastlı BT yardımıyla kitle ve damar yapıları daha iyi görülebilmektedir. Uygulanan kontrast madde öncelikle kalp, büyük damarlar, mediasten ve hiler bölgede tutulur. Tümör ve normal akciğer parankimi ise daha az oranda kontrast madde içerir. Böylece kitleye maksimum doz verilirken, normal dokular en iyi şekilde korunabilmektedir[5]. Öte yandan kontrast madde uygulaması BT kesitlerinin elektron yoğunluğunda değişime yol açmaktadır[5]. Tedavi sırasında hasta kontrast madde almayacağı için, kontrastlı BT kesitlerinin dansitesi tedavi esnasındaki dansiteden farklı olacaktır. Bu durum simülasyon esnasında elde edilen BT verilerine dayanarak yapılan doz hesaplamalarının doğruluğu hakkında şüphelere neden olabilir[6].

Akciğer kanseri için üç boyutlu RT tedavi planlamasında kontrast madde kullanımının etkileri ile ilgili çalışmalar giderek artmaktadır[5–7]. Biz de bu çalışmada akciğer kanseri nedeniyle YART planlaması yapılmış olan hastalarda, kontrastlı ve kontrastsız BT'ler ile doz hesaplanmasında kontrast maddenin etkisini incelemeyi amaçladık.

Materyal ve Metot

Bu çalışmada akciğer kanseri olan 10 hastanın YART planlama BT'leri retrospektif olarak değerlendirildi. Sekiz hasta küçük hücreli dışı akciğer kanseri, 2 hasta küçük hücreli akciğer kanseriydi. Hastaların hepsi erkekti. Ortalama yaş 64,5±10,2 (47–83) yıldı. Küçük hücreli akciğer kanseri olan hastalar sınırlı evre, küçük hücreli dışı akciğer kanseri olan hastalar ise evre 3 idi. Planlama BT'leri Phillips Brilliance CT Big Bore (Philips Medical Systems, Cleveland, OH, USA) tarayıcı ile yapıldı. Hastalara BT çekimi sırasında immobilizasyon aracı olarak Qfix (ArmShuttle Elite, Avondale, PA, USA) kullanıldı. Kontrast madde uygulaması planlama tomografisi çekiminin 20–22. saniyesinde otomatik enjektör (Medrad CT Vistron Injection System, One Medrad Drive, Indianola, PA, USA) yardımı ile yapıldı. Hastalarda tümörün yerleşimine göre 5, 6 ve 7 alan YART planlandı. Doz hesaplamaları planlanan hedef volüme (PTV) 30*200 cGy, toplam doz 60 Gy hedeflenerek tekrar düzenlendi. YART plan değerlendirilmesinde PTV'nin %95'inin, dozun %95'ini alması hedeflendi. Kontrastsız BT kesitlerinde yapılan YART planlamasında PTV'nin %50'sinin (D50), %90'ının (D90) ve %95'inin (D95) aldığı dozlar belirlendi. Daha sonra kontrastlı BT kesitleri üzerinde aynı alanlarla ve aynı öncelik değerleri kullanılarak YART planları tekrarlandı. Kontrastlı BT ile yapılan planlamalardan da tümör ve normal dokuların aldığı dozlar belirlendi. Kontrastlı ve kontrastsız dozlar karşılaştırıldı. Benzer olarak kritik normal yapılardan olan spinal kordun kontrastlı ve kontrastsız dozları da belirlenerek karşılaştırıldı. Ayrıca kritik normal yapılardan olan normal akciğer dokusunun 20 Gy ve üzerinde doz alan volümünün (V20) yüzdeleri de belirlenerek karşılaştırıldı.

Ayrıca kontrastlı ve kontrastsız dozların farkı hesaplandı. Doz farkı hesaplanırken, örneğin kontrastlı PTV D95'den, kontrastsız PTV D95 çıkartıldı ve sonuç cGy olarak bulundu. Kontrastlı ve kontrastsız görüntülere göre doz farkı yüzdesi (ΔD) aşağıdaki formül ile hesaplandı:

$$\Delta D = [(\text{kontrastlı hesaplanan doz}) - (\text{kontrastsız hesaplanan doz})] \times [(\text{kontrastsız hesaplanan doz}) \times 100]^{-1}$$

SPSS 15,0 istatistik programı istatistiksel analizler için kullanıldı. Değişkenlerin normallik analizi Shapiro-Wilk testi kullanıldı. Kontrastlı ve kontrastsız olarak PTV'nin aldığı dozların karşılaştırılması Paired *t*-testi ile değerlendirildi. Benzer olarak, kontrastlı ve kontrastsız olarak kritik normal dokuların aldığı dozların karşılaştırılması da Paired *t*-testi ile yapıldı. P değeri 0,05'den küçük ise istatistiksel olarak anlamlı kabul edildi.

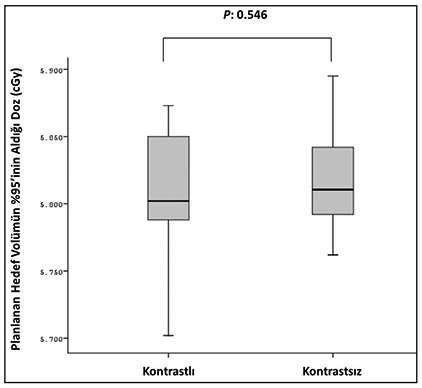
Bulgular

Tablo 1, PTV'nin aldığı dozların hesaplaması üzerine kontrast maddenin etkisinin değerlendirilmesini göstermektedir. Kontrastlı PTV D95 ve kontrastsız PTV D95 arasında anlamlı fark saptanmadı (p = 0,546) (Tablo 1 ve Şekil 1). Yine kontrastlı PTV D90 ve kontrastsız PTV D90 arasında anlamlı fark saptanmadı (p = 0,684) (Tablo 1 ve Şekil 2). Benzer olarak kontrastlı PTV D50 ve kontrastsız PTV D50 arasında da anlamlı fark saptanmadı (p = 0,134) (Tablo 1 ve Şekil 3).

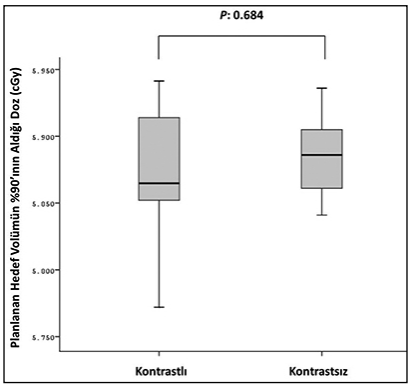
Tablo 1. *Planlanan tedavi volümünün doz hesaplaması üzerine kontrast maddenin etkisi*

PTV	Kontrastsız doz (cGy)	Kontrastlı doz (cGy)	Doz farkı yüzdesi (ΔD) (%)	P değeri
D95	5806 ± 51	5820 ± 39	-0.25 ± +1.21	0.546
D90	5868 ± 51	5877 ± 44	-0.14 ± +1.12	0.684
D50	6001 ± 45	6030 ± 31	-0.40 ± +0.78	0.134

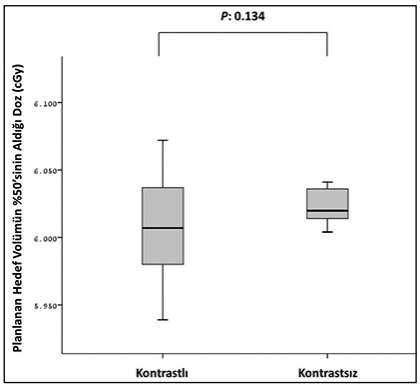
PTV: Planlanan tedavi volümü.



Şekil 1. *Planlanan hedef volümün %95'inin aldığı kontrastlı ve kontrastsız dozların karşılaştırılması.*



Şekil 2. *Planlanan hedef volümün %90'ının aldığı kontrastlı ve kontrastsız dozların karşılaştırılması.*

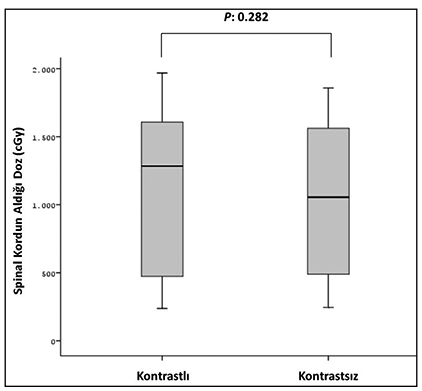


Şekil 3. *Planlanan hedef volümün %50'sinin aldığı kontrastlı ve kontrastsız dozların karşılaştırılması.*

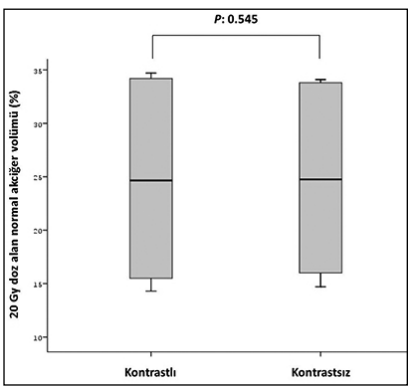
Tablo 2. *Kritik normal yapıların doz hesaplaması üzerine kontrast maddenin etkisi*

	Kontrastsız	Kontrastlı	Doz farkı yüzdesi (ΔD) (%)	P değeri
Spinal kord	1123 ± 580 cGy	1048 ± 592 cGy	+11.1 ± +33.1	0.282
Akciğer				
V20 (%)	25.0 ± 8.9	24.9 ± 8.3	+0.34 ± +3.4	0.545

V20, 20 Gy alan normal akciğer volümünün yüzdesini ifade etmektedir.



Şekil 4. *Spinal kordun aldığı kontrastlı ve kontrastsız dozların karşılaştırılması.*



Şekil 5. *20 Gy doz alan normal akciğer volümünün kontrastlı ve kontrastsız yüzdelerinin karşılaştırılması.*

Tablo 2, kritik normal yapıların (spinal kord ve normal akciğer dokusu) doz hesaplaması üzerine kontrast maddenin etkisinin değerlendirilmesini göstermektedir. Kontrastlı ve kontrastsız spinal kord dozları arasında anlamlı fark saptanmadı (p = 0,282) (Tablo 2 ve Şekil 4). Normal akciğer dokusunun kontrastlı ve kontrastsız V20 yüzdeleri arasında da anlamlı fark saptanmadı (p = 0,545) (Tablo 2 ve Şekil 5).

Tartışma

Kontrastlı BT görüntülemenin kullanımı tümör volümünün ve lenf nodlarının vasküler yapılardan ayrılmasına ve RT tedavi planlaması sırasında daha iyi çizilmesine olanak sağlar. Toraks akciğerin vasküler perfüzyonun fazla olması ve mediastendeki büyük vasküler yapılar nedeniyle kontrast madde kullanımı için en uygun alandır. Bu

vasküler yapıların kontrast madde kullanmaksızın tümör gibi yumuşak dokulardan ayırt edilebilmesi zor olabilir[6]. Öte yandan doz hesaplaması üzerine kontrast maddenin etkisi radyasyon tedavi planlamasında bazı endişeleri de beraberinde getirmektedir. Çünkü kontrast madde BT görüntülerinin dansitesinde değişime yol açmaktadır[5]. Tedavi sırasında hasta kontrast madde almayacağı için, kontrastlı BT kesitlerinin dansitesi tedavi esnasındaki dansiteden farklı olacaktır[6]. Kanserli hastalarda tedavi planı üzerine kontrast madde uygulamasının dozimetrik etkisi üzerine çalışmalar devam etmektedir. Shibamoto ve arkadaşları, çeşitli anatomik bölgelerdeki tümörler için BT kullanılarak yapılan RT planlanmasında doz hesaplaması üzerine kontrast maddenin etkisi incelemişlerdir. Kontrast madde kullanımının baş ve boyun, beyin, mediastinum ve pelvis tümörleri için tedavi planlanmasında doz hesaplamalarını anlamlı bir şekilde etkilemediğini gözlemlemişlerdir. Öte yandan üst abdominal ışınlama planlaması üzerine anlamlı bir etkisinin olduğunu ortaya koymuşlardır. Bunun özellikle karaciğer, dalak ve böbrek lokalizasyonları için geçerli olduğunu belirtmişler ve böylesi olgularda hem kontrastlı hem de kontrastsız görüntülerin alınmasını ve doz hesaplamalarının kontrastsız görüntüler üzerinde yapılması gerektiğini önermişlerdir[8].

Shi ve arkadaşları küçük hücreli dışı akciğer kanseri olan 9 hastanın BT ile tedavi planlaması sırasında uygulan kontrast maddenin foton radyasyon doz hesaplamaları üzerine etkisini incelemişlerdir. Bu araştırmacılar kontrastlı planlama ile kontrastsız planlama arasındaki doz farkının PTV için %2,5'den düşük olduğunu bulmuşlar ve kontrast madde kullanımının PTV'nin doz hesabı üzerine ihmal edilebilir bir etkisi olduğu sonucuna varmışlardır[7]. Benzer olarak, Lees ve arkadaşları da akciğer kanseri tedavi planlaması üzerine kontrast madde kullanımının minimal dozimetrik önemi olduğunu gözlemlemişlerdir[6]. Fayda ve arkadaşları küçük hücreli dışı akciğer kanserli bir hastanın kontrastlı ve kontrastsız BT kesitlerini XiO (CMS) ve Eclipse™ (Varian) sistemlerinde incelemişlerdir. Çeşitli alan boyutları ve açı düzenlemelerinde eşit ağırlıklı dozlar gönderilerek XiO'un konvolüsyon, Clarkson, hızlı süperpozisyon ve standart süperpozisyon ile Eclipse'nin modified Batho, Batho power law ve equivalent doku hava oranı (tissue air ratio, TAR) algoritmaları ile hesaplanan monitör ünitlerin kontrastla değişip değişmediğini değerlendirmişlerdir. Kontrast madde kullanımı ile monitor ünit değerlerinde ortalama + %1,3'lük (-%1 ile + %3,2 arasında) artış olduğunu bulmuşlardır. Sonuç olarak da kontrastlı BT kesitleri ile 3 boyutlu RT planlaması yapılabileceğini ama hedef hacimlerin kontrastlı kesitler üzerinde belirlenip, kontrastsız kesitlerle füzyonunun ve planlamanın kontrastsız kesitler üzerinde yapılmasının uygun olacağını önermişlerdir[5]. Bizim çalışmamızda da kontrastlı ve kontrastsız PTV doz hesaplamaları (D95, D90 ve D50) arasında anlamlı fark saptanmadı. Benzer olarak spinal kord ve normal akciğer dokusu gibi kritik normal yapıların kontrastlı ve kontrastsız aldığı dozlar arasında da anlamlı fark saptanmadı.

Bu bulguların özeti şudur; kontrast madde kullanımı damarların görüntülenmesini anlamlı bir şekilde değiştirmesine rağmen, doz hesaplaması üzerine çok az bir öneme sahiptir. Bu durumun birkaç nedeni olabilir. İlk olarak modern torasik RT'de multipl ışın hüzmesi kullanılmaktadır. Örneğin bizim çalışmamızda tümörün yerleşimine göre YART ile 5–7 ışın hüzmesi kullanıldı. Yine BT görüntüleme için kullanılan kontrast maddenin konsantarasyonu kan volümüne göre daha düşüktür. Bundan dolayı Hounsfield Unit (HU) değerindeki sonuç olarak elde edilen değişiklik de göreceli olarak düşüktür[7].

Bizim bulgularımız akciğer kanseri nedeniyle YART planlamasında kontrast madde kullanımının doz hesaplaması üzerine belirgin bir etkisinin olmadığını göstermiştir.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Reprodüktif Dönemde Anormal Uterin Kanaması Olan Kadınlarda Endometrial Poliplerin Obezite, Diyabet ve Hipertansiyon Sıklığı ile İlişkisi

The Relationship Between Endometrial Polyps, Obesity, the Incidence of Diabetes and Hypertension in Women Who Admitted with Abnormal Uterin Bleeding in Reproductive Ages

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ABSTRACT

Aim: *To investigate whether endometrial polyps are associated with obesity and incidence of diabetes mellitus or hypertension in women who admitted with abnormal uterin bleeding in reproductive ages.*

Material and Method: *We included 557 patients who had endometrial sampling due to the abnormal uterine bleeding. Patients with postmenopausal bleeding, endometrial hyperplasia or cancer and concomitant uterine pathology were excluded (n=117). Finally, endometrial polyp group consisted of 120 patients and control group consisted of 320 patients.*

Results: *Mean body mass index was statistically significantly higher in endometrial polyp group (30.1±2.94) compared to control group (28.2±1.92; p <0.001). The incidence of diabetes mellitus and hypertension was higher in endometrial group (8.33% and 6.67%) compared to control group (3.44% and 2.19%). The differences were also statistically significant (p = 0.031 and p = 0.021).*

Conclusion: *The results of our study reveal that, endometrial polyps are associated with higher body mass index and the presence of diabetes mellitus or hypertension. Not only in postmenopausal period or in cases of endometrial cancer; obesity, diabetes mellitus and hypertension may play a role in the etiopathogenesis of endometrial polyps.*

Key words: *endometrial polyps; obesity; diabetes mellitus; hypertension*

ÖZET

Amaç: *Anormal uterin kanama ile başvuran reprodüktif çağdaki kadınlarda, endometrial polip tanısının obezite, diyabet veya hipertansiyon sıklığı ile ilişkisi olup olmadığını araştırmak.*

Materyal ve Metot: *Anormal uterin kanama nedeni ile endometrial örnekleme yapılan 557 hasta çalışmaya dahil edildi. Postmenopozal kanaması olan, patoloji sonucunda endometrial hiperplazi veya kanser sapta-nan, eşlik eden uterin patolojisi bulunan hastalar çalışmadan dışlandı (n=117). Sonuç olarak endometrial polip grubu 120 hastadan oluşuyordu, kontrol grubu ise endometrial polip tanısı almamış 320 hastadan oluşturuldu.*

Bulgular: *Ortalama vücut kitle indeksi, endometrial polip grubunda (30,1±2,94), kontrol grubu (28,2±1,92) ile karşılaştırıldığında istatistiksel olarak anlamlı yüksekti (p <0,001). Diyabet ve hipertansiyon sıklığı yine endometrial polip grubunda (%8,33 ve %6,67) kontrol grubuna oranla (%3,44 ve %2,19) yüksek idi. Farklar istatistiksel olarak anlamlı idi (p = 0,031 ve p = 0,021).*

Sonuç: *Çalışmamızda elde ettiğimiz bulgulara göre, endometrial polipler obezite, diyabet veya hipertansiyon varlığı ile daha sık birliktelik göstermektedir. Sadece postmenopozal dönemde veya endometrial kanser varlığında değil, reprodüktif dönemde de obezite, diyabet ve hipertansiyon endomet-rial polip etyopatogenezinde rol alıyor görünmektedir.*

Anahtar kelimeler: *endometrial polip; obezite; diyabet; hipertansiyon*

Giriş

Endometrial polip (EP) endometriumdan köken alan, düzensiz endometrial bezler ve kalın duvarlı damarlar içeren, uterus lümenine doğru polipoid tarzda büyüyen, saplı olabilen bir lezyon olarak tanımlanır[1].

Endometrial polipler çoğunlukla asemptomatiktirler, bulgu vermezler. Semptomatik olduklarında ise en sık semptom anormal uterin kanama (AUK)'dır[2]. Her ne kadar EP etyopatogenezi tam olarak açıklanamamış olsa da hormonal faktörlerin etyopatogenezde önemli rol oynadığı düşünülmektedir[3,4].

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Literatürde yer alan bazı çalışmalarda endometrial poliplerin, obezite[5,6], diyabetes mellitus (DM)[6,7] ve hipertansiyon (HT) sıklığı[6,8] ile arttığı bildirilmiştir. Bazı çalışmalarda ise DM ile[5] ve HT sıklığı[5,9] ile ilişkisi saptanmamıştır.

Bu çalışmada, AUK ile polikliniğimize başvuran ve endometrial örnekleme yapılarak EP saptanan hastalar ile EP saptanmayan kontrol grubu hastaları arasında vücut kitle indeksi, DM ve HT sıklığı açısından fark olup olmadığını araştırıldı.

Materyal ve Metot

Bu kesitsel çalışmaya 2014 yılı Ocak ve Haziran ayları arasında polikliniğe AUK nedeniyle endometrial örnekleme yapılan reprodüktif dönemdeki (16–45 yaş) 475 kadın hasta dâhil edildi. En sık endikasyona neden olan AUK şekli menometroraji idi. Ayrıca polimenoresi ve hipermenoresi olan hastalara da endometrial örnekleme yapıldı. Bunların dışında AUK'ya neden olan endometrial örnekleme endikasyonları myoma uteri ve servikal polip idi. Eşlik eden konjenital uterin anomalisi olan (n=8) ve prematür ovaryen yetmezlik nedeniyle hormon replasman tedavisi veya meme kanseri nedeniyle tamoksifen (n=5) kullanan hastalar çalışma dışı bırakıldı. Histopatolojik olarak endometrial hiperplazi ve endometrium kanseri tanısı almış hastalar değerlendirmeye alınmadı (n=22). Sonuç olarak EP grubu 120 hastadan oluşuyordu, kontrol grubu ise EP tanısı almamış 320 hastadan oluşturuldu.

Tüm hastalara genel anestezi altında probe küretaj ile endometriyal örnekleme yapıldı. Bu nedenle çalışmamıza dahil edilen tüm hastaların işlemleri genel anestezi altında yapılmıştır. Hastaların operasyon öncesi demografik verileri, açlık glukoz değerleri, arteriyal tansiyon ölçümleri, vücut kitle indeksleri ve HT veya DM varlığı kayıt altına alındı. Kontrol grubunda histopatolojik tanılar: progesteron etkisinde endometrium, östrojen etkisinde endometrium, sekretuar endometrium ve profileratif endometrium ve normal endometrium idi.

Çalışma gruplarında, Tip 1 veya tip 2 DM tanısı açlık glukoz düzeyinin 126 mg/dL'den fazla olmasıyla kondu[10]. Daha önce DM tanısı almış ve DM tedavisi alan hastalar da çalışmaya dâhil edildi. HT tanısı iki arteriyal kan basıncı ölçümünün 140/90 mm Hg veya daha üstü olması ile kondu[11]. Yine daha önce HT tanısı almış ve HT tedavisi alan hastalar da çalışmaya dâhil edildi. Vücut kitle indeksi, kilonun (kg) boyun karesine (m^2) bölünmesi ile hesaplandı.

Verilerin analizi SPSS for Windows 20,0 paket programı ile yapıldı. Sürekli değişkenlerin dağılımının normale yakın olup olmadığı Shapiro Wilk testi ile araştırıldı. Sürekli değişkenler ortalama±standart sapma şeklinde, nominal değişkenler ise vaka sayısı ve (%) olarak gösterildi. Gruplar arasında ortalamalar yönünden farkın önemliliği student's t testi ile, nominal değişkenler ise ki-kare testi ile değerlendirildi. P <0,05 için sonuçlar istatistiksel olarak anlamlı kabul edildi.

Bulgular

EP grubunun yaş ortalaması 34,7±4,7 iken, kontrol grubunun yaş ortalaması 34,6±4,4 idi. İki grubun ortalama yaşları arasında istatistiksel anlamlı fark yoktu (p = 0,896). Gruplar arasında gebelik, doğum ve düşük sayıları açısından anlamlı fark bulunamadı (p = 0,384, p = 0,648 ve p = 0,667) (Tablo 1).

Ortalama vücut kitle indeksi, EP grubunda (30,1±2,9), kontrol grubu (28,2±1,9) ile karşılaştırıldığında istatistiksel olarak anlamlı yüksekti (p ≤0,001). DM ve HT sıklığı yine EP grubunda (%8,33 ve %6,67) kontrol grubuna oranla (%3,44 ve %2,19) istatistiksel olarak yüksek bulundu (p = 0,031 ve p = 0,021) (Tablo 2).

Tartışma

Her ne kadar EP etyopatogenezi net olarak ortaya konulamamış olsa da, histopatolojide karşımıza çıkan artmış endometrial bezler, artmış stromal dokular ve karakteristik polipoid görünümü veren spiral arter uzaması hormonal bozukluklar durumda endometriumda saptanan, sık görülen değişikliklerdir. Ek olarak endometrial poliplerin menarş öncesi görülmemesi ve sıklıkla eşlik eden bir hiperplazi bulunması hormonal faktörlerin etkili olduğu görüşünü desteklemektedir[12].

Sant'Ana de Almeida ve ark.[13] tarafından yapılan bir immunhistokimyasal çalışmada, polibe ait glandüler stromada ve polibe komşu endometriuma ait glandüler epitelde artmış östrojen ve progesteron reseptör ekspresyonu saptanmıştır. Polip stromasındaki östrojen reseptör ekspesyonu, polibe komşu endometriyal stromadaki ekspresyona oranla daha kuvvetli bulunmuştur. Yazarlar stromal ve epitel hücreleri arasındaki trofik etkili parakrin etkileşimin, epiteliyal östrojen üretiminin artmasına ve polip formasyonu oluşumuna neden olduğunu iddia etmişlerdir. Rutanen ve ark.[14] tarafından yapılan moleküler çalışmalarda, karşılanmamış aşırı östrojen maruziyetinin, dokularda başta insülin like growth faktör-1 (IGF-1) ve insülin like

Tablo 1. *Grupların demografik verilerinin karşılaştırılması*

	Endometrial polip grubu (n= 120)	Kontrol grubu (n= 320)	p değeri
Yaş	34,72±4,72	34,64±4,48	0,896*
Gebelik sayısı	3,73±2,2	3,94±1,7	0,384*
Doğum sayısı	2,86±1,86	2,95±1,35	0,648*
Düşük sayısı	0,34±0,73	0,31±0,61	0,667*

* Değerler "ortalama±standart sapma" şeklinde verilmiştir, karşılaştırmada kullanılan istatistik test ise student t test'tir.

Tablo 2. *Grupların vücut kitle indeksi, diyabet varlığı ve hipertansiyon varlığı açısından karşılaştırılması*

	Endometrial polip grubu (n= 120)	Kontrol grubu (n= 320)	p değeri
Vücut kitle indeksi (kg/m^2)	30,1±2,94	28,2±1,92	**<0,001***
Diyabet varlığı	10 (%8,33)	11 (%3,44)	**0,031****
Hipertansiyon varlığı	8 (%6,67)	7 (%2,19)	**0,021****

* Değerler "ortalama±standart sapma" şeklinde verilmiştir, karşılaştırmada kullanılan istatistik test ise student t test'tir.
** Değerler "hasta sayısı (yüzdesi)" şeklinde verilmiştir, karşılaştırmada kullanılan istatistik test ise ki kare testi'dir.

growth faktör-2 (IGF-2) olmak üzere çeşitli büyüme faktörlerinin anormal salınımına neden olduğu gösterilmiştir.

Obezite ve DM'da IGF-1 ve IGF-2'nin hem serumda hem de endometriyal dokuda anormal salınımının olduğu gösterilmiştir[14,15]. Büyüme faktörleri ve ilgili peptidlerin hedef dokularda otokrin ve parakrin mekanizmalar aracılığıyla hormonal aktiviteye aracılık ettiğine inanılmaktadır. Endometrial stromal hücreler IGF-1 ve IGF-2 gibi büyüme faktörlerinin yanı sıra IGF bağlayıcı protein (IGFBP) gibi yüksek afinite ile bu büyüme faktörlerini bağlayan ajanlar salgılamaktadır. Ayrıca bu hücreler IGF için membran reseptörleri ihtiva etmektedir. IGF-1 endometrium üzerinde gen ekspresyonunu artıcı, proliferatif, farklılaşmayı artıcı ve metabolik etkileri mevcuttur. Ayrıca IGF-1'in östrojen etkilerine aracılık ettiği kabul edilmektedir. IGF-2 gen ekspresyonu ise endometrial farklılaşmada rol oynamaktadır. İnsan endometriumundan salgılanan 6 farklı IGFBP'den en sık tespit edilen IGFBP-1'dir. Bu protein progesteron etkisi altındaki geç sekretuar faz endometriumundaki ve gebelik desiduasındaki stromal hücreler tarafından salınmaktadır. IGFBP, IGFBP-1'in endometrial hücrelere bağlanmasını ve bu hücrelerde meydana getirdiği metabolik değişiklikleri inhibe eder. Bu mekanizmadaki ana negatif düzenleyici insülindir ve insülin, IGFBP-1 transkripsiyonunu inhibe ederek etkinlik gösterir. Obezite ve DM meydana gelen hiperinsulinemi ile IGFBP'in IGFBP-1 üzerindeki inhibe edici etkisi ortadan kalkar ve endometrial dokunun IGFBP-1'e ve dolayısıyla metabolik sonuçlarına maruziyeti artar. Artan östrojenik ortam endometrial bezlerin ve stromanın proliferasyon ve farklılaşmasının artmasına neden olarak polip formasyonuna neden olmaktadır[14]. Bu çalışmada, EP saptanan hastalarda vücut kitle indeksleri ve DM sıklığı, kontrol grubu ile karşılaştırıldığında istatiksel olarak anlamlı oranda yüksek bulundu.

IGF, periferik ve koroner damarlarda nitrik oksit seviyelerini artırarak vazodilatatör aktiviteye sahiptir. Hipertansiyon varlığında serum IGF-1 düzeylerinin artışı daha önceki, çalışmalarda gösterilmiştir[16]. IGF vazodilatatör aktivesine karşın damarlar ve kalp üzerindeki inotropik ve hipertrofik etkisine bağlı olarak, hipertansiyon gelişimine katkı sağlıyor görünmektedir. Yukarıda bahsedildiği üzere, HT'unu bulunan hastalarda artan IGF düzeylerinin, endometrial doku üzerinde proliferasyon ve farklılaşmanın artmasına neden olarak polip formasyonuna neden olduğu düşünülebilir. Çalışmada hipertansiyon sıklığının, EP tanısı alan hastalarda istatistiksel olarak anlamlı oranda yüksek saptandı.

Obezite, DM ve HT varlığının endometrial kanser için birer risk faktörü olduğu günümüzde bilenen bir gerçektir. Ayabe ve ark.[17] tarafından yapılan çalışmada endometrium kanserli kadınların serum IGF-1 düzeylerinin kontrol grubuna nazaran daha yüksek olduğu saptanmıştır. Bu bulgu da obezite, DM ve HT varlığının

endometrial hücrelerde anormal proliferasyon ve farklılaşmaya neden olduğunun diğer bir kanıtıdır.

Literatürde kadınlarda %50'ye kadar varan endometrial polip sıklığı belirtilmişse de genel kanı görülme sıklığının %10 civarında olduğudur[18]. Bu çalışmada endometrial polip sıklığı, literatüre oranla yüksek bulunmuştur. AUK nedeniyle endometrial örnekleme yapılan hastaların dahil edilmesi ve bunun sonucu olarak semptomatik hastalarda organik bir patoloji olan EP ile karşılaşma olasılığının artması, yüksek insidansa neden olmuş olabilir.

TEKHARF çalışmasında[19], Türkiye'de reprodüktif yaştaki kadınlar arasında DM prevelansı %4,6 olarak rapor edilmiştir. Çalışmada kontrol grubunda DM sıklığı %3,44, EP grubunda ise %8,33 bulunmuştur. Ayrıca Hipertansiyon Prevalans Çalışması (PatenT)'nda[20] Türkiye'de reprodüktif yaştaki kadınlar arasında hipertansiyon sıklığı %11,5 bulunmuştur. Bu çalışmada hem kontrol hem de EP grubunda, HT sıklığı göreceli olarak daha düşük bulunmuştur (%2,19 ve %6,67) DM'un göreceli yüksek, HT'un ise göreceli düşük prevelanslarının, örneklem büyüklüğüne veya çalışma grubundaki hasta popülasyonun toplum içinden rastgele olarak değil, hastaneye başvuran zaten belli bir patolojiye sahip hastalar arasından seçilmesine bağlı olabileceği kanısına varıldı.

Bu çalışmada elde edilen bulgulara göre, EP varlığı obezite, DM veya HT varlığı ile daha sık birliktelik göstermektedir. Reprodüktif yaştaki kadınlarda EP'lerin obezite, DM, HT sıklığı ile ilişkisi randomize prospektif çalışmalarla araştırılıp desteklenmelidir.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Laparoskopik Sleeve Gastrektomide Stapler Hattının Güçlendirilmesi; Gerçekten Gerekli mi?

Buttressing the Stapler Line in Laparoscopic Sleeve Gastrectomy; Is It Really Necessary?

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ABSTRACT

Aim: *To evaluate the results of patients who underwent laparoscopic sleeve gastrectomy without buttressing the stapler line.*

Material and Method: *Hospital records of 16 consecutive patients who underwent laparoscopic sleeve gastrectomy without buttressing the stapler line between Jan 2014 and Dec 2015 were evaluated. Demographic datas, body mass index (BMI), operation time, pre-operative and post-operative (3rd day) hemoglobine levels and post-operative complications were evaluated.*

Results: *Mean age of patients was 44.1±7.2 and female tomale ratio was 12/4. Mean BMI was 49±9 kg/m^2. Mean duration of surgery was 87.9±16.1 minutes. Mean hemoglobin value was 14.41±0.77 gr/dL pre-operative and 13.91±0.82 gr/dL post-operative (3rd day). No major complication, leakage and bleeding was observed. All operations was ended witout conversion to open surgery.*

Conclusion: *All operations were done with new generation staplers without using any buttressing procedures and no complications occured. This study with small number of patients can be evaluated as a preliminary report.*

Key words: *laparoscopic sleeve gastrectomy; morbid obesity; stapler; leakage; bleeding*

ÖZET

Amaç: *Bu çalışmamızda morbid obezite nedeniyle laparoskopik sleeve gastrektomi uygulanan ve rezeksiyon hattına güçlendirme süturu konulmayan hastaların sonuçları değerlendirmeyi amaçladık.*

Materyal ve Metot: *Kliniğimizde Ocak 2014 ve Aralık 2015 tarihleri arasında morbid obezite nedeniyle laparoskopik sleeve gastrektomi uygulanan ve rezeksiyon hattına güçlendirme süturu konulmayan 16 ardışık hastanın dosyası incelendi. Hastaların demografik özellikleri, vücut kitle indeksi (VKİ), ameliyat süreleri, ameliyat öncesi ve ameliyat sonrası 3. gündeki hemoglobin (Hb) değerlerindeki değişim ve ameliyat sonrası gelişen komplikasyonları değerlendirildi.*

Bulgular: *Çalışmaya katılan hastaların ortalama yaşı 44,1±7,2, K/E oranı 12/4 idi. Hastaların ortalama VKİ 49±9 kg/m^2 olarak hesaplandı. Ortalama ameliyat süresi 87,9±16,1 dakika olarak hesaplandı. Ameliyat öncesi ortalama Hb değerleri 14,41±0,77 gr/dL, ameliyatın 3. gününde ortalama Hb değerleri 13,91±0,82 gr/dL olarak hesaplandı. Ameliyat sonrası hiçbir hastada major komplikasyon, stapler hattında kaçak veya kanama görülmedi. Tüm ameliyatlar açık cerrahiye geçilmeden laparoskopik olarak sonlandırıldı.*

Sonuç: *Kliniğimizde yeni nesil stapler ile rezeksiyon yaptıktan sonra hiçbir güçlendirici yöntem kullanmadık ve herhangi bir komplikasyon ile karşılaşmadık. Az sayıda vakamızla yayınladığımız bu çalışma bir ön sonuç olarak görülebilir.*

Anahtar kelimeler: *laparoskopik sleeve gastrektomi; morbid obezite; stapler; kaçak; kanama*

Giriş

Morbid obezite günümüzün en sık karşılaşılan sağlık sorunlarından birisidir. Cerrahi tedavi, özellikle de laparoskopik sleeve gastrektomi (LSG) en çok uygulanan yöntemlerden bir tanesidir. LSG'nin ameliyat sonrası yüz güldürücü sonuçları olmasına rağmen başta stapler hattından oluşan kaçak ve kanama gibi ciddi komplikasyonları mevcuttur. Bu komplikasyonların büyük oranda cerrahi teknikle ilişkili olduğu iyi bilinmektedir. Dikiş ve fibrin-yapıştırıcı ile stapler hattını güçlendirme gibi yöntemler önerilse de kesin olarak kabul edilen ve üstünlüğü kanıtlanmış bir yöntem yoktur. Literatürde dikiş hattını güçlendirecek yöntemler kullanılmasına rağmen kaçak oranının %7[1], kanama oranının ise %8,7'ye[2] ulaştığı bildirilmektedir. Ayrıca maliyeti arttırdığı ve ameliyat süresini de uzattığı bir gerçektir[3,4]. Bu çalışmamızda, LSG esnasında yeni nesil stapler ile rezeksiyon yapılan ve sonrasında hiçbir güçlendirici yöntem kullanmayan hastaların sonuçlarını değerlendirdik.

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Materyal ve Metot

Kliniğimizde Ocak 2014 ve Aralık 2015 tarihleri arasında morbid obezite nedeniyle başvuran ve laparoskopik sleeve gastrektomi uygulanan 16 hastanın dosyaları retrospektif olarak değerlendirildi. Tüm hastalar ameliyat öncesi karar verilirken endokrinolog, diyetisyen ve genel cerrahiden oluşan multidisipliner konseyde değerlendirildi. Ayrıca tüm hastalar konsey öncesi bir psikiyatrist ile birebir görüştüler. Uygun görülen hastalar ameliyat için yönlendirildi. Tüm hastaların vücut kitle indeksi (VKİ) 40 kg/m^2'nin üzerinde veya 35 kg/m^2'nin üzerinde olup obeziteye bağlı ek hastalıkları mevcuttu. Ameliyat öncesi, kardiyak ve pulmoner kapasiteleri açısından değerlendirildi, gastroskopi ve batın ultrasonografileri yapıldı. Ameliyatların hepsi aynı cerrah tarafından (L.A.) aynı teknik ile gerçekleştirildi. Çıkarılan tüm spesmenler değerlendirilmek üzere patolojiye gönderildi. Çalışmaya dahil edilen hastaların demografik özellikleri, VKİ, ameliyat süreleri, ameliyat öncesi ve ameliyat sonrası 3. gündeki hemoglobin (Hb) değerlerindeki değişim ve ameliyat sonrası gelişen komplikasyonları değerlendirildi.

Cerrahi Teknik

Tüm hastalardan ameliyat öncesi yazılı onam formu alındı. Ameliyattan 1 gece önce düşük molekül ağırlıklı heparin ile tromboflaksi yapıldı ve anti-embolik çorap giydirildi. Tromboflaksiye ameliyat sonrası 3 hafta daha devam edildi. Ameliyat öncesi 1 gr ampicilin/sulbaktam ile antibiyo-proflaksi uygulandı. Hastalar supin pozisyonunda uyutulup bıçaksız trokar ile laparoskopik görüş altında göbekten 10 mm'lik kamera portu girilerek 10–12 mmHg basınca ulaşana kadar insüflasyon yapıldı. Daha sonra ters Trandelenburg pozisyonu verildi ve çalışma portları yerleştirildi. Omentum damar mühürleme cihazı ile (LigaSure™ 5 mm blunt, LF1637) pilorun yaklaşık 3–5 cm proksimalinden başlanarak His açısına kadar mideden ayrıştırıldı. Daha sonra özellikle mide arka yüzü ve fundus düzeyi tamamen serbestleştirildikten sonra orogastrik yolla 32 F silikon mide tüpü yerleştirildi. Pilor proksimalinde (Crow's foot seviyesinden başlayarak) His açısına kadar endoskopik stapler yardımıyla mide diseke edildi. Bu aşamada küçük antrum bırakılmasına, düz bir hatta (ön ve arka duvar eşit ende olacak şekilde) dar bir tüp oluşturulmasına özen gösterildi. Antrumda kalın dokuya uygun stapler (Endo GIA™ 60 mm ArticulatingExtra-ThickReloadwithTri-Staple™ Technology), midenin geri kalan kısmında ise orta kalınlıkta dokulara uygun stapler (Endo GIA™ 60 mm ArticulatingMedium/ThickReloadwithTri-Staple™ Technology) kullanıldı. Mide ayrıştırıldıktan sonra orogastrik kalibrasyon tüpü çekildi ve dikiş hattında kanama kontrolü yapıldı. Kanama görülürse laparoskopik klip ile sadece o bölge kliplenerek hemostaz sağlandı. Lümen içine nazogastrik tüp yerleştirildi ve kaçak testi için prepilorik bölge barsak pensi ile klempe edilip mavi boyalı serum fizyolojik (~80 cc) nasogastrikten verildi. Tüpleştirilen mide beyaz gazlı bezle stapler hattı boyunca kontrol edildi. Kaçak kontrolü sonrası dikiş hattına paralel bir adet aspiratif dren yerleştirildi. Ameliyatın birinci gününde mavi boyalı su içirilerek drenden kaçak kontrolü yapıldı, nazogatrik tüp çekildi.

Bulgular

Toplam 16 hasta çalışmaya dahil edildi. Çalışmaya katılan hastaların ortalama yaşı 44,12±7,21 (33–58 yaş arası), K/E oranı 12/4 idi. Hastaların ortalama VKİ 49±9,20 kg/m^2 (35–63 arası) olarak hesaplandı. VKİ'si 40'ın altında olan 4 hastada tip 2 diyabet ve hipertansiyon nedeniyle ameliyat kararı alındı.

Ortalama ameliyat süresi 87,9±16,13 dakika (60–118 dakika arası) idi. Ameliyat sonrası ortalama hastanede kalış süresi ise 4,43±0,72 gün (4–6 gün arası) olarak bulundu. Ortalama dren kalış süresi 2,12 gün (2–3 gün arası) ve ortalama dren debisi 52,5±34,3 cc olarak hesaplandı. Ameliyat öncesi ortalama Hb değerleri 14,41±0,77 gr/dL, ameliyatın 3. gününde ortalama Hb değerleri 13,91±0,82 gr/dL olarak hesaplandı. Hastaların hiç birisinde 1 gr/dL'nin üzerinde düşüş saptanmadı.

Ameliyat sonrası hiçbir hastada major komplikasyon, stapler hattında kaçak veya kanama görülmedi. Tüm ameliyatlar açık cerrahiye geçilmeden laparoskopik olarak sonlandırıldı.

Tartışma

Laparoskopik sleeve gastrektomi günümüzde en sık uygulanan bariatrik cerrahi tekniktir[5,6]. Teknik olarak Roux-en-Y gastrik bypass'a oranla çok daha rahat olması ve ayarlanabilir gastrik bant uygulamasındaki gibi yabancı cismin getireceği komplikasyonlardan uzak olması gibi avantajlarının yanında sadece kilo kaybını sağlamayıp metabolik iyileşmeye de katkı sağlaması daha fazla tercih edilen yöntem olmasını sağlamıştır[7].

Bariatrik cerrahi klavuzlarına[8] uygun olarak ameliyat edilen tüm hastalar detaylı bir multidisipliner konseyde kararlaştırıldıktan sonra ameliyata alındı. Ameliyat öncesi hastaların ortalama VKİ 49±9,20 kg/m^2 (35–63 arası) olarak hesaplandı. VKİ'si 40'ın altında olan 4 hastaya ise ek hastalıkları (tip 2 diyabet ve hipertansiyon) nedeniyle ameliyat kararı alındı.

Literatür incelendiği zaman ortalama ameliyat sürelerinin artan deneyim ve vaka sayısı ile azaldığı görülmektedir. Consten ve ark.'nın 2004 yılında yaptığı 20 hastalık bir çalışmada ameliyat süresi 210±14 dakika olarak saptanırken[3], Dapri ve ark.'nın yaptığı 75 hastalık bir çalışmada ise 47±10,7 dakika olarak saptanmıştır. Kendi serimizde ortalama ameliyat süresi 87,9±16,13 dakika (60–118 dakika arası) olarak saptandı. Kendi deneyimimizde de artan ameliyat sayımız ile ameliyat süresinin azaldığını görmekteyiz.

LSG'de stapler kullanımı vazgeçilemezdir ve stapler kullanılarak yapılan ameliyatlar arasında en uzun dikiş hattı LSG'de oluşturulur. Bu uzun dikiş hattının da beraberinde getirdiği iki önemli komplikasyon vardır; dikiş hattından kaçak ve kanama. Bu komplikasyonları engellemeye yönelik birçok yöntem denenmiştir ama maalesef komplikasyon olasılığını ortadan kaldıracak bir teknik tanımlanmamıştır. Dikiş hattının ayrışması mekanik (teknik) ve iskemik sebeplerden dolayı meydana gelir. Mekanik sebeplerden oluşan kaçaklar ilk 48 saat içinde oluşurken iskemi kaynaklı ayrışmalar inflamatuar ve fibrotik yanıtın en yoğun olduğu 5–7. günler arasında olur[9]. Dikiş hattından olan kanamayı ve ayrışmayı önlemek için birçok yöntem denenmiştir. Simon ve ark.'nın 59 hastada SeamGuard (W. L. Gore&Associates, Flagstaff, AZ) ile dikiş hattını güçlendirdiği, 80 hastada ise güçlendirici kullanmadığı çalışmasında ameliyat sonrası kaçak oranları eşit bulunmuştur[10]. Dapri ve ark.'nın çalışmasında ise SeamGuard'ın stapler hattından kanamayı azalttığı fakat kaçak üzerine bir etkisi olmadığı saptanmıştır[4]. Diğer bir yöntem olan fibrin yapıştırıcılar da birçok yazar tarafından denenmiş fakat onda da çelişkili sonuçlar elde edilmiştir. Aydın ve ark.'nın çalışmasında fibrin yapıştırıcı kullanımının kaçak oranını azaltmadığı, ameliyat süresi ve maliyetini arttırdığı bildirilmiştir[11]. Gentileschi ve ark. da Aydın'a benzer sonuçlar bulmuşlardır[12]. Musella ve ark. ise fibrin yapıştırıcı kullanılan hastalarda daha az kanama olduğunu savunmuşlardır[13].

Stapler hattından kaçak ve kanamayı önlemek için başvurulan bir diğer yöntem ise stapler hattına dikiş konulmasıdır. Shashank ve ark. yaptıkları çalışmada dikiş hattına konulan güçlendirici sütürlerin (Peri-StripsDry with Veritas) kanama sıklığını ve ciddiyetini azalttığını ve ameliyat süresini kısalttığını belirtmişlerdir[14]. Ameliyat süresindeki kısalmayı da hattan olan kanamaya tek tek konulan sütürlerin daha fazla zaman almasına bağlamışlardır. Çalışmalarında hiçbir hastada kaçak gelişmediği için kaçak hakkında bir yorumda bulunmamışlardır. Ancak Parikh ve ark.'nın 9991 hastayı değerlendirdiği bir meta-analizde güçlendirici sütürlerin kaçak yönünden bir katkı sağlamadığı belirtilmiştir[15]. Sroka ve ark.'nın çalışmasında, stapler hattının fibrin yapıştırıcı ve sütür ile güçlendirildiği iki grup kontrol grubu ile karşılaştırılmış[16]. Sütür grubunda hiç kanama saptanmazken, fibrin yapıştırıcı grubunda %4, kontrol grubunda ise %10 oranında Hb değerlerinde >2 gr/dL düşüş saptanmış. Bizim serimizde ise hiçbir hastada Hb değerlerinde >1 gr/dL düşüş saptanmadı. Literatürden farklı olarak düşüş saptanmamasının sebebinin yeni nesil stapler kullanılması ve stapler hattında görünen kanama odaklarının hemoklip yardımı ile tek tek kliplenmesi olduğunu düşünmekteyiz.

Çalışmamızın kısıtlılıklarının başında retrospektif bir çalışma olması ve vaka sayısının az olması gelmektedir. Ancak bildiğimiz kadarıyla güncel literatürde yeni nesil staplerler kullanılarak yapılmış böyle bir çalışma yer almamaktadır. Ayrıca tek cerrah tarafından, aynı teknik uygulanarak yapılması homojenite açısından iyi fakat çalışmanın daha yavaş ilerlemesine sebep olmaktadır. Çalışmanın devamının bir kontrol grubu ile birlikte prospektif, randomize geniş vaka serili olarak yapılması planlanmaktadır.

Stapler hattından olan kanama ve kaçakları önlemek için dikişle ve fibrin-yapıştırıcı ile güçlendirme gibi yöntemler kullanılsa da kesin olarak kabul edilen ve üstünlüğü kanıtlanmış bir yöntem yoktur. Biz kliniğimizde yeni nesil stapler ile rezeksiyon yaptıktan sonra hiçbir güçlendirici yöntem kullanmadık ve herhangi bir komplikasyon ile karşılaşmadık. Az sayıda vakamızla yayınladığımız bu çalışmada bir ön sonuç olarak; Tri-Staple teknolojisinin dokuya uygun manipülasyonla uygulanmasının hem hemostazı hem de doku birleşmesi güvenliğini artırdığı söylenebilir.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Relationship between Treatment Response and Histological Scoring Systems Applied in Chronic Hepatitis B

Kronik B Viral Hepatitlerde Kullanılan Histolojik Skorlama Sistemleri ile Tedavi Başarısı Arasındaki İlişkinin Saptanması

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ABSTRACT

Aim: *In patients with chronic viral hepatitis liver biopsy has more important role in treatment planning than diagnostics. Nowadays, the role of liver needle biopsies is to provide a qualitative rather than a quantitative assessment of effects of viral hepatitis. For this qualitative assessment three scoring systems (Modified Knodell, METAVIR, Scheuer) are more widely used and the scoring results has become requisite in the pathology reports. The aim of this study is to identify the relationship between histopathological parameters of scoring systems applied in chronic viral hepatitis and treatment response; together with a comparison of these results with the literature.*

Material and Method: *101 patients diagnosed to have chronic B viral hepatitis and followed up for at least one year were included in the study. Patients were divided in two clinical groups according to the response to antiviral therapy. The relationship between treatment response and histological parameters of three scoring systems (Modified Knodell, Scheuer, METAVIR) used in chronic viral hepatitis were statistically evaluated.*

Results: *There appeared to be a statistically significant relationship between the treatment response and METAVIR total grade A, METAVIR lobular activity in chronic B viral hepatitis.*

Conclusion: *It can be claimed that METAVIR scoring system is better than Modified Knodell system for his-tological assessment in chronic B viral hepatitis.*

Key words: *viral hepatitis; scoring; HBV*

ÖZET

Amaç: *Kronik B viral hepatitlerde karaciğer biyopsisi tanısal öneminden çok tedavi planlamasında önemlidir. Günümüzde karaciğer biyopsileri viral hepatitlerin niceliksel özelliklerinden çok niteliksel etkilerini saptamak için yapılmaktadır. Bu niteliksel değerlendirme için üç skorlama sistemi (Modifiye Knodell, Scheuer, METAVIR) daha sık kullanılmaktadır. Skorlama sonuçlarının patoloji raporlarında yazılması zorunlu olmuştur. Bu çalışmadaki amaç, kronik B viral hepatitlerde uygulanan skorlama sistemlerindeki histopatolojik parametrelerin tedavi başarısı ile ilişkisinin araştırılması ve literatür bilgileri ile karşılaştırılmasıdır.*

Materyal ve Metot: *En az bir yıl süreyle takip edilen ve Hacettepe Üniversitesi Tıp Fakültesi Patoloji Anabilim Dalı ile Gastroenteroloji Bilim Dalında kronik B viral hepatit tanısı almış 101 hasta çalışmaya dahil edilmiştir. Hastalar antiviral tedaviye yanıt açısından iki gruba bölünmüştür. Kronik viral hepatitlerde kullanılan üç skorlama sistemini (Modifiye Knodell, Scheuer, METAVIR) oluşturan parametrelerin tedavi başarısı ile ilişkisi istatistiksel olarak araştırıldı.*

Bulgular: *Kronik B viral hepatitlerde METAVIR total grade A ve METAVIR lobüler aktivitesi ile tedavi yanıtı arasında istatistiksel olarak anlamlı sonuç saptandı.*

Sonuç: *Bu çalışmada kronik B viral hepatitlerde histopatolojik değerlendirmede METAVIR skorlama sisteminin Modifiye Knodell sistemine tercih edilmesinin daha uygun olduğu saptanmıştır.*

Anahtar kelimeler: *viral hepatit; skorlama; HBV*

Introduction

In patients with chronic viral hepatitis (CVH) liver biopsy has more important role in treatment planning than diagnostics. Nowadays, the role of liver needle biopsies is to provide a qualitative rather than a quantitative assessment of effects of viral hepatitis. For this qualitative assessment three scoring systems (Modified Knodell, METAVIR, Scheuer) are more widely used[1,2,3] (Table 1–4) and the scoring results has become requisite in the pathology reports**.** Reliability,

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Table 1. *Modified knodell scoring system*

Necroinflammatory scores	
A) Periportal or periseptal interface hepatitis (piecemeal necrosis)	
Absent	0
Mild (focal, few portal areas)	1
Mild/moderate (focal, most portal areas)	2
Moderate (continous around <50% of tracts or septa)	3
Severe (continous around >50% of tracts or septa)	4
B) Confluent necrosis	
Absent	0
Focal	1
Zone 3 nekrosis in some areas	2
Zone 3 nekrosis in most areas	3
Zone 3 nekrosis + occasional portal-central (P-C) bridging	4
Zone 3 nekrosis + multiple P-C bridging	5
Panacinar or multiacinar nekrosis	6
C) Focal ("spotty") lytic necrosis, apoptosis, and focal inflammation	
Absent	0
One focus or less per 10x objective	1
Two to four foci per 10x objective	2
Five to ten foci per 10x objective	3
More than ten foci per 10x objective	4
D) Portal inflamation	
Absent	0
Mild, some or all portal areas	1
Moderate, some or all portal areas	2
Moderate/severe, all portal areas	3
Severe, tüm portal alanlar	4
Total Modified HAI	18
STAGING: Architectural changes, fibrosis and cirrhosis	
No fibrosis	0
Fibrous expansion of some portal areas, with or without short fibrous septa	1
Fibrous expansion of most portal areas, with or without short fibrous septa	2
Fibrous expansion of most portal areas with occasional portal to portal (P-P) bridging	3
Fibrous expansion of portal areas with marked bridging (portal to portal (P-P) as well as portal to central (P-C)	4
Marked bridging (P-P and/or P-C) with occasional nodules (incomplete cirrhosis)	5
Cirrhosis, probable or definite	6
Maximum fibrosis score	6

Additional features which should be noted but not scored: Bile-duct inflammation and damage, lymphoid follicles, steatosis (mild, moderate or marked), Hepatocellular dysplasia (large- or small-cell), adenomatous hyperplasia, iron or copper overload, intracellular inclusions (eg. PAS-positive globules, Mallory bodies).
Immunohistochemical findings: Information on viral antigens, lymphocyte subsets or other features, when available, should be recorded and may be semi-quantitatively expressed.

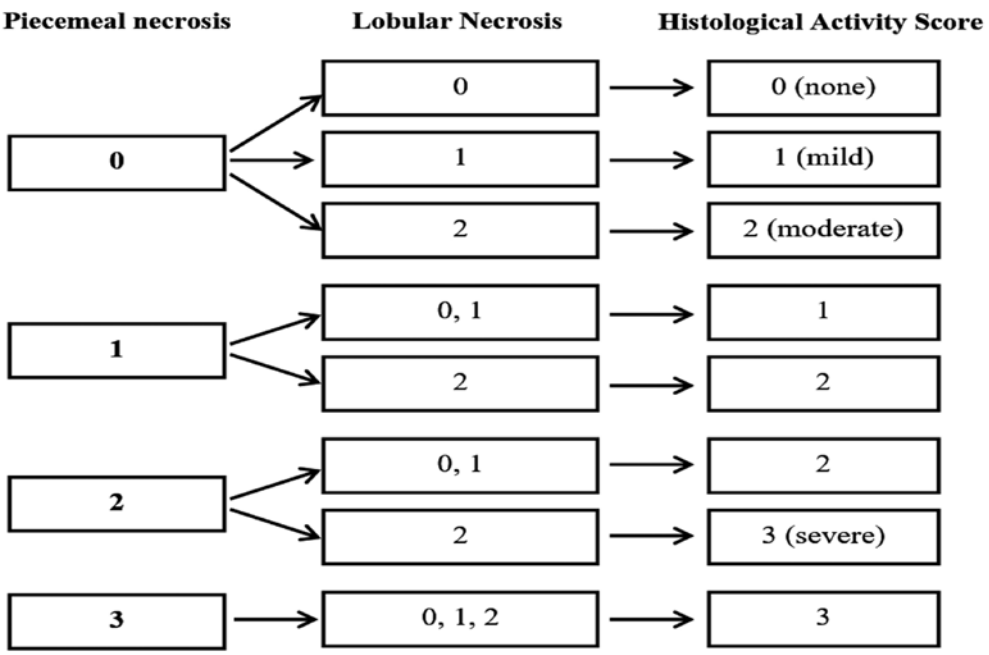
Table 2. *Scheuer Scoring System*

NECROINFLAMMATORY ACTIVITY		
Grade	Portal/periportal activity	Lobular activity
0	None or minimal	None
1	Portal inflammation	Inflammation but no necrosis
2	Mild piecemeal necrosis	Focal necrosis or acidophil bodies
3	Moderate piecemeal necrosis	Severe focal cell damage
4	Severe piecemeal necrosis	Damage includes bridging necrosis
FIBROSIS AND CIRRHOSIS		
0	None	
1	Enlarged, fibrotic portal tracts	
2	Periportal or portal-portal septa, but intact architecture	
3	Fibrosis with architectural distortion but no obvious cirrhosis	
4	Probable or definite cirrhosis	

Table 3. *METAVIR Scoring System*

Piecemeal necrosis	
0	None
1	Focal, some portal areas
2	Focal, all or diffuse, some portal areas
3	Diffuse, all portal areas
Lobular necrosis	
0	<1 foci per lobule
1	At least 1 foci per lobule
2	Multiple foci per lobule

Table 4. *Algorithm for evaluation histological activity (METAVIR)*



meaning, reproducibility of these parameters vary in different scoring systems. In addition, there are difficulties in determining the cut-off values of these parameters for treatment decision making in our country. These problems often encountered in our daily practice, raise the need to examine the role of scoring systems in treatment decision making. In this study, the different scoring systems in chronic hepatitis B (CHB) are investigated in order to predict treatment outcome and to assess the importance of histologic parameters in treatment decision making.

Material and Method

Patient Selection

Retrospectively reported liver needle biopsies in Hacettepe University, Faculty of Medicine, Department of Pathology between the years 2005–2009 were identified from database of our hospital. Patients with a complete clinical data and clinical follow up for at least 1 year, and to whom therapy has been started after biopsy were included in the study. There is no unique scoring system for CHB. Antiviral therapy choice for

CHB was nucleoside or nucleotide analogues and any interferon therapy was excluded in these patients to get a homogenous group.

Clinicopathological criteria were definite, adequacy of biopsy for evaluation, i.e. a minimum of 1.5 cm and a minimum of six tracts[4], absence of medication intake and/or absence of secondary diseases (multiple myeloma, malignancies, lymphoproliferative diseases, inflammatory bowel disease, rheumatoid arthritis etc.) treatment outcomes of which can affect liver biopsy evaluation. Combined infection of HBV+HDV or HBV+HCV infections were excluded in the study group.

9 patients with CHB with a clinical follow-up prior to 2005 attuned to criteria were also included to this study. As a result, 101 CHB providing full compliance with these criteria are included to the study.

Histopathological Assessment

Five micron sections made after average 24 hours fixation in 10% formalin, processing and paraffin embedding, were examined by H-E, trichrome, Prussian blue and Gomori methenamine silver (reticulin) stains. In this study, Modified Knodell, METAVIR, Scheuer's scoring systems were used by one pathologist (SA) appropriately for both grading (the evaluation of hepatocellular damage and necroinflammatory changes) and staging (degree of fibrosis).

Patients with cirrhosis (Modified Knodell score 6 and METAVIR/Scheuer score 4) were not included in this study. For this reason statistical evaluation of staging depended on 0–5 points in Modified Knodell classification and 0–3 points in METAVIR/Scheuer classification.

Criteria for Treatment Success

Patients were divided into two groups (successful and unsuccessful) according to the compliance for the success criteria based according to accepted international and national guidelines[5,6].

Goal of antiviral therapy in HBeAg-negative CHB is the reduction or extinction of HBV-DNA value, which is defined as virological response and normalization of aminotransferase levels is defined as biochemical response. Success in CHB treatment was defined as virological, biochemical and, if any, histological response after 48 weeks of therapy. Partial response, viral and biochemical breakthrough under antiviral therapy were classified as unsuccessful treatment response. Because of the different antiviral agents, it was not possible to further classify the patients according to receiving the single antiviral agent. However, patient follow ups and determination of HBV DNA levels were performed and recorded according to current guidelines.

For statistical analysis Statistical Package for the Social Sciences (SPSS) software, version 17.0 (SPSS, Chicago, Illinois, USA) was used. Univariate analysis has been done.

Results

Patients' Characteristics

There were 32 female and 69 male patients. Median age was 38.1 (min: 18, max: 67). 71 of 101 cases (% 70.3) comply with the success criteria and 30 cases (% 29.7) do not. The distribution of patients according to the compliance of treatment success criteria are given in Table 5.

Scoring systems: Findings Related to Necroinflammatory Activity

We have encountered no confluent necrosis among the patients with CHB according to Modified Knodell scoring system. Therefore, in statistical studies total HAI score was reduced from 18 to 12. There was no statistically significant relationship between total HAI score and treatment success ($p > 0.05$) (Table 6). The contribution of three parameters (interface hepatitis, lobular activity, portal inflammation) of this scoring system to the treatment response was also not statistically significant ($p > 0.05$) (Table 6).

The relationship between total METAVIR grade and treatment response was statistically significant ($p = 0.008$). To study this result, two parameters constituting total METAVIR histological activity grade (interface hepatitis and lobular activity) and treatment response were analyzed separately. There was significant relation between higher lobular activity and higher treatment success ($p = 0.005$) (Table 7).

There were no statistically significant relation between the parameters of Scheuer`s scoring system which is taken up as third scoring system and treatment (portal inflammation in all cases $p=0.36$ and lobular activity $p = 0.732$) (Table 8).

Scoring Systems: Findings Related to Staging

There was no statistical relation between treatment success and degree of fibrosis in any of the scoring systems used (METAVIR, Modified Knodell and Scheuer scoring system) ($p > 0.05$).

Discussion

The first classification of chronic hepatitis was described by De Groote J et al. in 1968[7]. Then, the specification of viral factors, increase in diagnosis and treatment options gave birth to the necessity of new classifications. According to the scoring system proposed by Knodell et al. evaluation was made by 4 categories and then degree gained by the collected points was defined as hepatic activity index (HAI)[8], However, combined evaluation of fibrosis (stage) and inflammatory changes (grade), combined evaluation of two parameters (periportal inflammation and bridging necrosis) with different pathogenesis[9–11,] furthermore mathematical problems related to nonsuccessive sequence in scoring system time to time posed a problem for pathologists. Then Ishak et al. accepted confluent necrosis as the fourth criterion in necroinflammatory evaluation and stage has started to be defined separately[2]. Hepatocyte damage seen in "piecemeal necrosis" is thought as apoptosis rather than lytic necrosis[12]. So this finding was approved as interface hepatitis. Afterwards, different authors published new scoring methods in the literature. Examples of these scoring methods are Scheuer, French METAVIR group, Kenneth Batts and Jurgen Ludwig scoring systems[1,3,13].

The most important problem in evaluation of different histological activity scoring systems in CVH is intraobserver and interobserver variation[14–17]. Common feature of the studies in the literature is the low interobserver and intraobserver error rate in staging; but this rate declines when scoring systems become more difficult to apply. The most important factors that can affect these studies are the experience of specialist, the qualitative and quantitative characteristics of the specimen and microscopy application techniques at low and high magnification[14,18,19]. Another example of problems in scoring is total score in Modified Knodell scoring system. For the reason that these total score is given via four different parameters, these values may not represent the severity of disease. For example, Modified HAI score 9 in two different patients may not consist of the same parameter scores or the course may not be the same.

METAVIR scoring system is presented in the literature as the scoring system experienced by interobserver compatibility rather than persons'own experiences between scoring systems[1,20,21]. Most widely used in Europe, this is an algorithmic approach system rather than simple scoring system as Modified Knodell system. There are important articles with different comments on all scoring systems in the literature[21–28].

For antiviral therapy, lamivudine and/or nucleos (t) ide analogue drugs were used in CHB cases of our study. We accepted treatment success as the sole criterion and did not separate our patients into groups according to the drugs used. In general, studies in the literature analyzed treatment response in therapy groups which used certain medicines. The main goal in many of these studies is to determine appropriate therapy and medicine protocol (industrial result). Our starting point in this study is to determine morphologic criteria affecting patient therapy (academic benefit) far from industry.

There is hardly any study in the literature investigating relation between treatment response and parameters constituting score rather than relation with the total score. Such studies may allow to revision or simplification of scoring systems. We tried to assess parametric approach in the foreground rather than total scoring system.

Table 5. *Distribution of treatment response*

	Successful	Unsuccessful	Total
HBV	71 (%70.3)	30 (%29.7)	101 (%100)

Table 6. *Modified Knodell criteria and treatment success in CHB*

Histopathologic feature	p values
Interphace hepatitis	0.291
Lobular activity	0.116
Portal inflammation	0.663
Total Histologic Activity Index score excluding confluent necrosis (total score 0-12)	0.540
Knodell Stage	0.683

Table 7. *Metavir criteria and treatment success in CHB*

Histopathologic feature	p values
Interphase hepatitis	0.343
Lobular activity	0.005
Histologic activity grade	0.008
Metavir stage	0.310

Table 8. *Scheuer criteria and treatment success in CHB*

Histopathologic feature	p values
Interphase hepatitis	0.253
Lobular activity	0.316
Metavir stage	0.310

In our department we use Modified Knodell scoring system due to therapy planning of CHB according to reimbursement system by Social Security Institution of Turkish Republic. Evaluating biopsies according to this system we see that confluent necrosis parameter constituting an important point (6 points) in the system, impact the histopathological score negatively due to its descriptive rather than qualitative nature. It's known that this type of necrosis is a finding frequently seen in acute/subacute or autoimmune hepatitis rather than CVH[25]. Confluent necrosis was not seen in any patient neither in our current study nor in the studies known in the literature[15,19] or seen in a few (1/363 cases)[1]. So, confluent necrosis was ignored by us. Albeit confluent necrosis is a parameter of scoring system, our own experience showed it's useless in evaluation of CVHs. Looking from this point of view, it's seen that Modified Knodell total HAI score automatically drops from 18 to 12. However in this way Modified Knodell scoring system becomes more feasible in terms of intraobserver and interobserver studies. We believe that removal of confluent necrosis which is seen infrequently in CVH from current scoring system or using scoring systems not including confluent necrosis in the routine practice will be more appropriate. At the national level, therapy planning according to activity index leads to the formation of an untreated patient group. Because decision of therapy starting at Modified Knodell HAI score 7 is admitted on the basis of total score of 18. Author's own experience is that the rarity of confluent necrosis may preclude some patients from the therapy who may benefit and this arbitrary cut-offs dictated by government or insurance agencies may leave out some candidates for good response. Exclusion of confluent necrosis from scoring system drops total score to 12 and so necessitates lowering of the treatment starting score. This problem does not create any important change in the staging evaluation.

In staging studies comparing two different fibrosis (staging) classification systems proposed by Knodell and Scheuer, reproducibility is higher in the simpler staging method as Scheuer fibrosis evaluation[15]. The point to be taken into account is that reproducibility of staging in Modified Knodell scoring system is low but it has more descriptive information[25] and application simplicity. In general, the more complex systems have the capability to provide more information than simple ones but are less reproducible[25]. In conjuction with interobserver agreement problems in current staging systems we have to know that 7 point (Modified Knodell) and 5 point (METAVIR, Scheuer) staging systems can easily be interconverted.

There are many studies in the English literature investigating predictive factors for treatment response in CHB. The common point in these publications[29,30] is the evaluation of morphological improvement criteria is performed according to the Knodell Scoring system. This scoring system is not in use today. Furthermore, the two point drop in control biopsies were taken as the criterion for improvement. Considering the interobserver or intraobserver compliance variation, we have doubt about the sufficiency of these two points as a parameter of treatment response. Another feature to note here is that cases had been evaluated by one pathologist and evaluation of control biopsies after treatment was performed after a certain time from the first biopsy so interobserver variation is inevitable. In our own study, for eliminating the interobserver or intraobserver compliance variation treatment success parameter had been generated out of clinical parameters.

Another study investigating predictive factors in CHB is performed by Shindo M et al. In this study, fibrosis was selected as the histopathologic parameter. Morphological grading was performed according to Knodell classification (excluding fibrosis) and fibrosis evaluation (staging) according to 5 point system. In multivariate analysis, high grade and low fibrosis were identified as important predictive factors for treatment response. The treatment response was better in low fibrosis stage in interferon-treated patients. In addition, in these patients necroinflammatory activity was seen as an important factor. There was no difference in terms of treatment response between stage 1–2 and stage 3–4 in lamivudin-treated patients[31].

In our study three scoring systems commonly used in the world was compared with clinical treatment success regardless of drugs used for antiviral treatment. Only METAVIR lobular activity and total grade have relation with treatment response ($p < 0.05$) in CHB; treatment success rate increases as lobular activity and total grade increase. This finding supports treatment indication in cases with higher histologic grade. However, there is not enough information about this in the English literature. Generally, studies have been based on the Knodell or Modified Knodell system. Unlike our application (as noted above in our department and in our country we apply Modified Knodell scoring system), METAVIR system is more meaningful in clinicopathologic evaluation.

Finally, we know that pretreatment histological assessment is important for treatment planning in CHB. We think that routinely applied Modified Knodell system will create more problems than METAVIR system.

In this study it was seen that METAVIR scoring system is more adequate than Modified Knodell system in treatment decision making in CHB, and staging used for treatment planning is not a predictive factor.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Pediatrik Hastalarda Manyetik Rezonans Görüntüleme Sırasında Uygulanan Anestezi Deneyimlerimiz

Anesthesia Experiences During Magnetic Imaging Process on Pediatric Patients

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ABSTRACT

Aim: *We aim to study the quality of sedation and complications ratios during anesthesia applied with sodium thiopental and propofol and the reason of the magnetic imaging requests on pediatric patients retrospectively according to the hospital data.*

Material and Method: *In this study, 109 patients, aged from 3 months to 5 years, that have been applied magnetic imaging process under anesthesia, have been examined retrospectively.*

Results: *Pentotal sodium has been applied to 53 patients and propofol has been applied to 56 patients. Anesthesia processes were successfully performed on both groups.*

Conclusion: *We recommend that pentothal sodium and propofol anesthesia can be used safely for outpatient anesthesia during magnetic imaging studies under appropriate physical and technical circumstances.*

Key words: *pediatric patients; magnetic imaging process; sodium thiopental; propofol*

ÖZET

Amaç: *Çalışmamızda pediatrik hastalarda manyetik rezonans görüntüleme istem nedenleri, pentotal sodyum ve propofol ile yapılan anestezi uygulamalarının sedasyon kalitesini, komplikasyon oranlarını geriye dönük olarak incelemeyi amaçladık.*

Materyal ve Metot: *Bu çalışmada Kafkas Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesinde 2013–2016 yılları arasında 3 ay – 5 yaş aralığındaki pediatrik hastalarda anestezi altında çekilen manyetik rezonans görüntüleme işlemi uygulanan 109 hasta retrospektif olarak incelendi.*

Bulgular: *Kayıtları incelenen 109 hastanın 53'üne pentotal sodyum, 56'sına propofol uygulandığı saptandı. Her iki grupta komplikasyon olmadan anestezinin tamamlandığı tespit edildi.*

Sonuç: *Günübirlik ameliyathane dışı anestezi uygulamalarında özellikle manyetik rezonans görüntüleme işlemi esnasında gerekli fiziki ve teknik altyapının düzenlenmesinden sonra pentotal sodyum ve propofolün güvenli bir şekilde uygulanabileceği kanısındayız.*

Anahtar kelimeler: *pediatrik hastalar; manyetik rezonans görüntüleme; pentotal sodyum; propofol*

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Giriş

Günümüzde yüksek görüntü kalitesi ve bilinen bir zararının olmaması nedeniyle klinisyenler tarafından tanı amaçlı manyetik rezonans görüntüleme (MRG) istemi giderek artmaktadır. Optimum görüntü sağlanabilmesi için görünteleme esnasında tam bir hareketsizlik gerekmektedir. Bu nedenle hareketsiz kalamayan, zihinsel özürlü olan, klostrofibisi bulunan çocuklarda ve erişkinlerde sedasyon veya genel anestezi uygulamaları gerekli olmaktadır[1]. Ameliyathane dışı uygulamalar anestezistler için özel sorunlar ve potansiyel komplikasyonları beraberinde getirmektedir. Ameliyathane dışında kullanılan ajanlarla yapılan anestezik işlemlerde hasta idamesinde vital fonksiyonların stabil olması, anestezi sonrası hastanın çabuk uyanması, hızlı derlenme, derlenme sonrası fizik ve mental aktivitelerin en kısa sürede normale dönmesi ve taburculuğu geciktirecek bulantı, kusma, baş dönmesi ve ağrı gibi yan etkilerin olmaması çok önemli yer tutmaktadır[2].

Biz çalışmamızda 2013–2016 yılları arasında pediatrik hastalarda manyetik rezonans görüntüleme istem sebepleri ve ameliyathane dışı anestezi işlemleri sırasında kliniğimizce uygulanan anestezi tekniklerini ve ortaya çıkan komplikasyonları sunmayı amaçladık.

Materyal ve Metot

Kafkas Üniversitesi Uygulama ve Araştırma Hastanesinde 2013–2016 yılları arasında tanısal amaçlı MRG işlemi için anestezi uygulaması yapılan 109 pediatrik hastanın dosyaları retrospektif olarak incelendi. Hastaların MRG istem sebepleri, uygulanan anestezi yöntemleri ve gelişen komplikasyonlar incelendi. MRG ünitesinde MRG uyumlu anestezi cihazı (Aestiva/5MRI, Datex/Ohmeda, Helsinki, Finland) ile hasta başı monitörü (S/5 MRG monitör; Datex-Ohmeda, Helsinki,

Finland) kullanıldığı görüldü. Olgulara işlem öncesinde damar yolu açıldığı ve midazolamla premedikasyon uygulandığı tespit edildi. Tüm hastalarda non invaziv kan basıncı, solunum sayısı, kalp atım hızı ve periferik oksijen satürasyon takibinin beş dakikada bir yapıldığı görüldü. Kalp hızı değerlendirmesinde Tablo 1'de gösterilen değerler normal olarak kabul edildi (Tablo 1).

Kalp hızı normalin %25 altında ise bradikardi olarak değerlendirilip atropin (0,02 mg/kg) intravenöz yol ile tedavi edildiği gözlendi. Periferik oksijen satürasyonu %90'ın altı desatürasyon olarak kabul edildi ve başın pozisyonun değiştirilmesi, airway uygulaması ve/veya maske ile oksijen verilerek tedavi edildiği gözlendi.

MRG uygulaması sırasında olgulara sedasyon amacıyla anestezik ajan olarak 2,5 mg/kg sodyum tiyopental ya da propofol 2 mg/kg propofol iv yolla verildiği gözlendi. Çekim sırasında hareketlenme görülen hastalara tiopental sodyum 1 mg/kg ya da 0,5 mg/kg propofol iv yolla eklendiği gözlendi. İşlem sonrası olguların derlenme odasına alındığı Aldrete skorlama sistemi ile takip edildiği tespit edildi. Aldrete skorları 9 ve üstü olan hastaların servise çıkarıldığı tespit edildi. Derlenme ünitesinde ve serviste görülen komplikasyonlar incelenen dosyalardan kayıt edildi.

Bulgular

Kayıtları incelenen 109 hastanın 53'üne pentotal sodyum, 56'sına propofol uygulandığı saptandı (Tablo 2). MRG istem sebepleri incelendiğinde 51 adet beyin MRG, 4 adet kulak MRG, 12 adet kalça MRG, 23 adet lomber-servikal MRG, 15 adet ekstremite MRG istendiği anlaşıldı (Tablo 3). Propofol uygulanan 2 hastada bradikardi, 2 hastada desatürasyon, 2 hastada uzamış sedasyon, 1 hastada bulantı-kusma, 5 hastada işlem esnasında ek ilaç ihtiyacı, pentotal sodyum uygulanan 3 hastada bradikardi, 4 hastada desatürasyon, 5 hastada uzamış sedasyon, 7 hastada bulantı-kusma, 2 hastada işlem esnasında ek ilaç ihtiyacı olduğu saptandı (Tablo 4).

Tartışma

MRG tanı amaçlı kullanılan non-invaziv bir işlem olup diğer görüntüleme yöntemlerine göre iyonize radyasyon kullanmaması nedeni ile hastalar için belirgin avantaj sağlar. MRG'da görüntüler herhangi bir vücut planında sağlanması ve yumuşak doku kontrastının daha üstün olması diğer görüntüleme yöntemlerinden farkıdır[2]. Bu ünitelerde cihazın güçlü manyetik alan olması sebebiyle bu ünitelere özel olarak üretilmiş ekipman ve monitöre ihtiyaç vardır.

Görüntü alınan bölgenin hareketsiz olması MRG işleminde görüntü kalitesinin artmasında çok önemli bir yer tutar. Pediatrik hastalarda MRG işleminin başarılı olabilmesi hareketsizlik ve kooperasyonun sağlanabilmesine bağlı olduğundan anestezik yöntemlerin uygulanması gerekmektedir. Ancak ameliyathane dışı anestezi uygulamaları; anestezistler ve hastalar açısından kullanılan anestezik ajanların etkileri, cihaz ve ekipman özellikleri, sebebiyle daha riskli girişimler olarak kabul görmektedir. Bu işlemlerin kendileri çocuklara küçük riskler oluştururken, sedasyon ve analjezi verilmesi de önemli riskler ilave eder. Bu durum özellikle MRG gibi işlemler sırasında özellik arz eder. MRG işlemi sırasında çocuklar korkabileceklerinden derin sedasyon verilmesi gerekir[3]. MRG'de sedasyon için tiyopental, propofol, ketamin, midazolam, etomidat, fentanil gibi ajanlar kullanılır[4]. Biz de

Tablo 1. *Olguların hemodinamik değerleri için kullanılan normal sınırlar*

Yaş	Kalp hızı (atım/dk)	SKB/DKB (mmHg)
3–12 ay	120	95/65
1–6 yaş	100	100/70

DKB; diyastolik kan basıncı, SKB; sistolik kan basıncı

Tablo 2. *Yaş gruplarına göre ilaç seçimi*

	3 ay – 1 yaş	1–2 yaş	2–3 yaş	3–4 yaş	4–5 yaş	Toplam
Pentotal sodyum	8	11	15	17	2	53
Propofol	3	6	18	21	8	56

Tablo 3. *MRG istem nedenleri*

Beyin MR	Kulak MR	Kalça MR	Lomber-servikal MR	Ekstremite MR	Toplam
51	4	12	23	19	109

Tablo 4. *Komplikasyon oranları*

	Pentotal sodyum	Propofol
Bradikardi	3	2
Desatürasyon	4	2
Uzamış sedasyon	5	2
Bulantı/kusma	7	1
Ek ilaç ihtiyacı	2	5

kliniğimizde MRG tetkiki için anestezi uygulanacak pediatrik olgularda midazolam, tiopental sodyum ve propofol kullanmaktayız.

Tiyopental, oldukça hızlı indüksiyon sağlayan ve pediatrik anestezi uygulamalarında tercih edilen bir ajandır. Kardiyovasküler sistemi ve solunumu baskılayabilmektedir. Glasier ve ark. tiyopental sodyumu MR çekilecek çocuklarda rektal yoldan uygulamışlar ve hastaların %96'nda başarılı bir sedasyon sağlamışlardır[5]. Bizim kliniğimizde pentotal sodyum uygulanan 3 hasta desatüre oldu baş pozisyonunun değiştirilmesi ve airway uygulamasıyla yeterli oksijenlenme sağlandığı gözlendi. Propofol çabuk metabolize olması, birikme özelliğinin olmaması nedeniyle hızlı bir derlenme sağlaması ve bulantı-kusma sıklığının diğer ajanlara göre daha az olması sebebiyle günübirlik hastalarda sıklıkla tercih edilmektedir[6]. Bizde kliniğimizde propofol uyguladığımız hastalarda güvenli bir şekilde sedayon sağladık.

Sonuç olarak, günübirlik ameliyathane dışı anestezi uygulamalarında gerekli fiziki ve teknik altyapının düzenlenmesinden sonra pentotal sodyum ve propofolün güvenli bir şekilde uygulanabileceği kanısındayız.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Abdominopelvic Pain: A Prospective Study of 137 Patients

Abdominopelvik Ağrı: 137 Olgunun Prospektif Çalışması

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ABSTRACT

Aim: *This prospective study aims to evaluate the role of diffusion-weighted magnetic resonance (DW-MR) imaging in patients presenting with acute abdominopelvic pain, who are decided a follow-up with conservative treatment after admission in the emergency department.*

Material and Method: *A total of 137 consecutive patients with various causes of acute abdominopelvic pain were followed-up with DW-MR imaging to monitor the response to medical treatment after a primary diagnosis made by combination of DW-MR imaging and computed tomography (CT).*

Results: *The demography of study population was as follows: mean age, 49.8; range, 19–84 years: 72 females, 65 males. For each follow-up DW-MR imaging review, the decision was made by three radiologists in consensus. All data regarding follow-up DW-MR imaging, clinical symptoms and laboratory results were documented. A total of 283 DW-MR scans were performed; 273 DW-MR scans were compatible with the clinical status, while 10 were disconcordant with the clinical status. 11 patients needed a CT scan and 16 patients underwent surgery.*

Conclusion: *DW-MR imaging is a non-invasive and efficient technique that may be used with confidence to monitor patients with non-operated acute abdominopelvic pain during follow-up.*

Key words: *acute abdominopelvic pain; computed tomography; diffusion-weighted magnetic resonance imaging; emergency department*

ÖZET

Amaç: *Bu prospektif çalışmada, difüzyon ağırlıklı manyetik rezonans (DAG-MR) görüntülemenin akut abdominopelvik ağrı ile acil servise baş vuran ve konservatif tedavi ile takip kararı verilen olgulardaki rolünün araştırılması amaçlanmaktadır.*

Materyal ve Metot: *Toplam 137 olguda DAG-MR ve bilgisayarlı tomografi (BT) kombinasyonu ile ilk tanı konulduktan sonra, takipte tedavi yanıtı DAG-MR ile değerlendirildi.*

Bulgular: *Çalışma popülasyonu; ortalama yaş 49,8, yaş aralığı 19–84, 72 kadın ve 65 erkek şeklinde idi. Takipte toplamda 283 DAG-MR tetkiki yapıldı. Bunlardan 273 tanesi klinik bulgular ile uyumluyken, 10 tanesi uyumsuzdu. 11 olguda BT ihtiyacı olurken, 16 tanesi opere edildi.*

Sonuç: *DAG-MR görüntüleme invazif olmayan, etkili bir yöntem olup akut abdominopelvik ağrılı olguların takibinde güvenli bir şekilde kullanılabilir.*

Anahtar kelimeler: *akut abdominopelvik ağrı; bilgisayarlı tomografi; difüzyon ağırlıklı manyetik rezonans görüntüleme; acil servis*

Introduction

Computed tomography (CT) has been used both as the primary diagnostic imaging method and follow-up imaging method for acute abdominopelvic pain. However, with increased demand of CT scans, concern has been put on limitations, especially those about radiation induced potential risk of malignancy, contrast induced allergic reactions, and contrast induced nephrotoxicity[1].

Ultrasonography (USG) is imaging method, generally as a first-line tool, in the most acute clinical managements, especially in children and pregnant women. On the other hand, it has some limitations in solving complex disease processes[2,3].

Magnetic resonance (MR) imaging has become an alternative imaging method for acute abdominopelvic pain in emergency departments. There are many reviews regarding the utility of MR imaging for assessment of acute abdominopelvic pain. The advantages of MR imaging include, being free of ionizing radiation and not using iodinated contrast agent[4–6].

Diffusion-weighted MR (DW-MR) imaging has been increasingly used for such emergencies. Diffusion relies on the priciple of different degrees of mobility of molecules, primarily water molecules, among different

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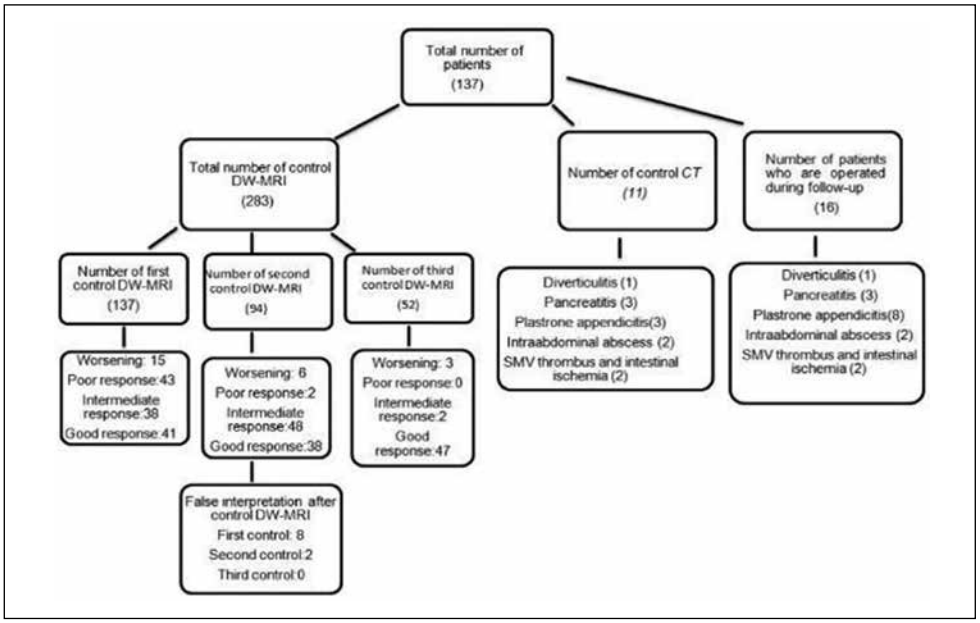

Figure 1. *Patient flow diagram (DW-MRI: diffusion weighted imaging, CT: computed tomography, SMV: superior mesenteric vein).*

tissues at cellular level. It is inversely related to cellularity, cell membrane integrity, and lipophilicity. Tumors, abscesses, fibrosis, and cytotoxic edema lead to restricted diffusion[7–9].

To our knowledge, this is the first study that analyses the utility of DW-MR imaging monitoring the non-operated patients with various causes of acute abdominopelvic pain to assess the response to medical treatment. We hypothesize that the use of DW-MR imaging for follow-up of non-operated patients with acute abdominopelvic pain can reduce unnecessary CT scans that might be needed in the follow-up, and thus reducing radiation dose. We also think that DW-MR is an efficient method of imaging for monitoring the response to medical treatment.

Material and Method

Patient Selection and Inclusion Criteria

Between October 2014 and May 2015, a total of 137 consecutive non-operated patients presenting with various causes of acute abdominopelvic pain were followed-up with DW-MR imaging to monitor the response to medical treatment after a primary diagnosis was made with the combination of DW-MR imaging and computed tomography (CT) in the emergency department. Acute abdominopelvic pain was characterized as a sudden pain starting within a few days with typical clinical and laboratory findings such as pain on palpation, rebound, and rise of the acute phase reactants with elevation of white blood cell count. In our study, we included clinically stable patients who were started medical therapy rather than emergency surgery by the desicion of attending surgeon in charge. Children under the age of 16, pregnant women, patients who underwent surgery after the initial diagnosis, extremely unstable patients, and those who were not suited for MR imaging (e.g. claustrophobia, pacemaker, rejected consent, etc.) were excluded from the study. All the patients were clinically stable and decided to be followed up conservatively. The study sample were as follows: mean age, 49.8; range, 19–84 years; 72 females (52.5%), 65 males (47.4%). The patient flow diagram is shown at Figure 1.

In the follow-up, all patients underwent DW-MR, varying from 1 to 3 times, and 11 of them (8%) needed a CT scan. Follow-up of these patients was discontinued after a two-months of non-symptomatic period. Approval from the hospital ethics committee and informed consents from all patients were obtained.

Imaging Protocols

DW-MR examinations were made on a 1.5-T MR imaging unit (Magnetom® Aera; Siemens, Erlangen, Germany). DW-MR imaging was performed on all patients after the first 10-days of medical treatment period.

The DW-MR protocol consisted of an axial diffusion-weighted single-shot echoplanar sequence with fat suppression, without breath holding (TR (time to repeat), 7500; TE (time to echo) 62–80 ms; matrix, 192x192; slice thickness, 5 mm; gap, 6 mm; FOV, 400 mm; PAT factor 2; b values: 0, 500, and 1000 s/mm^2; scanning time, 3 min). An additional DW-MR was performed on the patients who needed a control scanning after a 10-day period. The time for a control DW-MR scan ranged between 10 to 30 days. Patients who developed complications had an additional contrast enhanced CT scan. CT was performed with a 16-slice multidetector-row scanner (Toshiba Alexion™/Advance, Toshiba Medical Systems Corporation Nashu, Japan).

Image and Statistical Analysis

All examinations were reviewed prospectively in consensus by three radiologists with at least 5 years of experience in abdominal imaging interpretation. The readers were aware of the initial diagnosis and consecutive clinical-laboratory findings.

The DW-MR images were evaluated in an independent workstation (Syngo. via, Siemens). Three b values (0, 500, and 1000) were used, and on images with the highest b value, a bright signal was considered to be positive for regions of interest. Three different apparent diffusion coefficient (ADC) values were calculated using region of interest (ROI) placed centrally, and the mean was measured.

Follow-up DW-MR images were interpreted according to disease progress, and scored as those that have worsening, poor or little response, intermediate response, and those with good response. The parameters used for scoring were, the size and ADC values for the specific disease. Patients who developed complications had an additional contrast enhanced CT scan. CT was performed with a 16-slice multidetector-row scanner (Toshiba Alexion™/Advance, Toshiba Medical Systems Corporation Nashu, Japan) pathology on DW-MR scans. An increase of size with or without ADC decrement was accepted as worsening, a rate less than 10% decrease in size with little or no ADC increment was accepted as poor response, a decrease of size between 10–50% with ADC increment was accepted as intermediate response, and decrease of size more than 50% with ADC increment was accepted as good response. DW-MR was repeated after 10-day period when the response was either poor or little. A CT scan was performed when patients had clinical and laboratory worsening.

C-reactive protein (CRP) level, white blood cell (WBC) count, amylase level, urine analysis, fever, and abdominal pain were the major parameters used for assessment of the clinical status, depending on the pathology.

Results

The results are shown at Table 1. The mean follow-up time was 5.6±2.4 months (range: 2.1–10.8). After a 10-day period, all patients underwent DW-MR imaging. 94 patients needed a second DW-MR (68%), and 52 patients (37.9%) needed a third DW-MR, after a 10-day period. A total of 283 DW-MR scans were performed. The evaluation of treatment response with each DW-MR imaging were as follows: 1. worsening in 24 (8.4%), 2. poor or little response in 45 (15.9%), 3. intermediate response 88 (31%), and 4. good response in 126 (44.5%). 255 (90%) DW-MR scans revealed improvement compatible with the clinical status.[18] DW-MR scans (6.3%) showed worsening in concordance with clinical status. 6 (2.1%) and 4 (1.4%) DW-MR scans had worsening and improvement, respectively disconcordant with the clinical status. All patients who underwent a CT scan, had either poor-little or intermediate response on DW-MR imaging. A CT scan was performed on a total of 11 patients (8%). A total of 16 patients (11.6%) underwent surgery.

Discussion

A quick decision making on the basis of clinical and laboratory evaluation in acute abdominopelvic pain is essential to avoid unnecessary interventions as well as a delay of diagnosis of serious emergencies[10]. It has been reported that imaging in acute abdominopelvic pain increases the accuracy of the clinical diagnosis, influences decision making about management, and increases the diagnostic certainty in patients with acute abdominopelvic pain[11]. USG and CT are the most widely used imaging tools for acute abdominopelvic pain, both at presentation and in follow-up period.

Sonographer dependency, obesity, abdominal gas, and inefficiency to solve complicated disease processes are the disadvantages of USG. On the other hand, USG is a simple and cheap imaging method that is particularly useful in children and pregnant women[12,13].

Increased demand of CT scans in emergency departments has led concern on limitations, especially those about radiation induced potential risk of malignancy,

Table 1. *Diagnoses and imaging results of the patients*

Diagnosis	Number and frequency	DW 1.	DW 2.	DW 3.	Control CT	Surgery
Cholecystitis	26 (18.9%)	26 (1 W, 4 P, 7 Int, 14 G, 1 F)	12 (0 W, 0 P, 5 Int, 7 G, 1 F)	5 (0 W, 0 P, 0 Int, 5G, 0 F)	-	-
Pyelonephritis	20 (14.5%)	20 (0 W, 2 P, 6 Int, 12 G, 0 F)	8 (0 W, 0 P, 2 Int, 6 G, 0 F)	2 (0 W, 0 P, 0 Int, 2 G, 0 F)	-	-
Diverticulitis	19 (13.8%)	19 (2 W, 2 P, 8 Int, 7 G, 1 F)	12 (1 W, 0 P, 3 Int, 8 G, 0 F)	4 (1 W, 0 P, 0 Int, 3 G, 0 F)	1	1
Pancreatitis	15 (10.9%)	15 (4 W, 9 P, 0 Int, 2 G, 1 F)	12 (2 W, 0 P, 10 Int, 0 G, 1 F)	12 (2 W, 0 P, 0 Int, 10 G, 0 F)	3	3
Plastron appendicitis	15 (10.9%)	15 (2 W, 6 P, 7 Int, 0 G, 2 F)	15 (1 W, 1 P, 6 Int, 7 G, 0 F)	7 (0 W, 0 P, 2 Int, 5 G, 0 F)	3	8
Infammatory bowel disease	12 (8.7%)	12 (1 W, 9 P, 2 Int, 0 G, 1 F)	12 (0 W, 0 P, 10 Int, 2 G, 0 F)	10 (0 W, 0 P, 0 Int, 10 G, 0 F)	-	-
Intraabdominal abscess	10 (7.3%)	10 (2 W, 6 P, 0 Int, 2 G, 0 F)	8 (2 W, 0 P, 6 Int, 0 G, 0 F)	6 (0 W, 0 P, 0 Int, 6 G, 0 F)	2	2
SMV thrombus and intestinal ischemia	8 (5.8%)	8 (3 W, 3 P, 2 Int, 0 G, 2 F)	7 (0 W, 1 P, 4 Int, 2 G, 0 F)	4 (0 W, 0 P, 0 Int, 4 G, 0 F)	2	2
Mesenteric panniculitis	7 (5.1%)	7 (0 W, 1 P, 4 Int, 2 G, 0 F)	5 (0 W, 0 P, 1 Int, 4 G, 0 F)	1 (0 W, 0 P, 0 Int, 1 G, 0 F)	-	-
Epiploic appendagitis	5 (3.6%)	5 (0 W, 1 P, 2 Int, 2 G, 0 F)	3 (0 W, 0 P, 1 Int, 2 G, 0 F)	1 (0 W, 0 P, 0 Int, 1 G, 0 F)	-	-

DW: MR Findings, W: worsening, P: poor response, Int: intermediate response, G: good response, F: False interpretation

contrast induced allergic reactions, and contrast induced nephrotoxicity[1,14]. There are many studies in the literature pointing the importance regarding the attempts to reduce radiation dose in CT scans[15–18]. It seems logical that CT scans performed in the follow-up for monitoring some of the patients with non-operated acute abdominal pain, will increase the radiation exposure. This is the major concern pointed in our study.

Recent advances in MR imaging has led to increased number of use in emergency departments for acute abdominopelvic pain. Free of ionizing radiation and no need of iodinated contrast agent are the advantages of MR imaging[3,4,6,15,19,20]. DW-MR imaging in the abdomen is now widely used. DW-MR relies on the principle of different degrees of mobility of molecules, primarily water molecules, among different tissues at cellular level. Diffusion is inversely related to cellularity, cell membrane integrity, and lipophilicity. Restricted diffusion is observed in tissues with high cellularity (e.g. tumors, abscesses, fibrosis, and cytotoxic edema). The images are obtained in short intervals without the need of contrast agent. With generation of ADC maps, quantitative analysis can be made with different b values. At least 2 b values are needed for DW imaging analysis, and itis well known that the greater number of b values improves the accuracy of calculated ADC[6,19,21–24]. We used 0, 500, and 1000 as the standart b values in our study.

Our study population consisted of patients who were admitted to the emergency department, with a specific diagnosis as a cause of abdominopelvic pain made by both DW-MR and CT imaging. It was decided that these patients would be followed-up without the need of an operation at presentation. We aimed to follow-up these non-operated patients with DW-MR to monitor the response to medical treatment. All reviews were made with consensus by three radiologists. 11 of 137 patients (8%), who developed unavoidable clinical and laboratory worsening needed a CT scan. A total of 294 scans (283 DW-MR and 11 CT scans) were performed in the overall follow-up periods. Knowing the fact that only 11 CT scans (5.6% of total scans) were inevitable, it is obvious that we precluded most of the CT scans, thus reducing ionizing radiation.

In our study, in patients with superior mesenteric vein (SMV) thrombosis, DW-MR revealed both the thrombus and the ischemic changes of bowel, hence allowing to monitor the thrombus as well as the ischemia during thrombolytic and antibiotic medications (Figure 2). Our patients with plastron appendicitis were screened with DW-MR for optimum timing of operation (Figure 3). It was also found to be a good predictor for monitoring treatment response for pancreatitis (Figure 4).

This study has several limitations. Low spatial resolution of DW-MR imaging, short time interval for follow-up, and lack of use of another imaging modality for comparison were the major limitations of our study. We also haven not included other MR sequences that may provide morphological information which could have better idenified the lesion borders, especially with the use of IV contrast. However, the inclusion of other MR sequences would go against our aim in this study as we tried to implement the quickest MR method without the use of IV

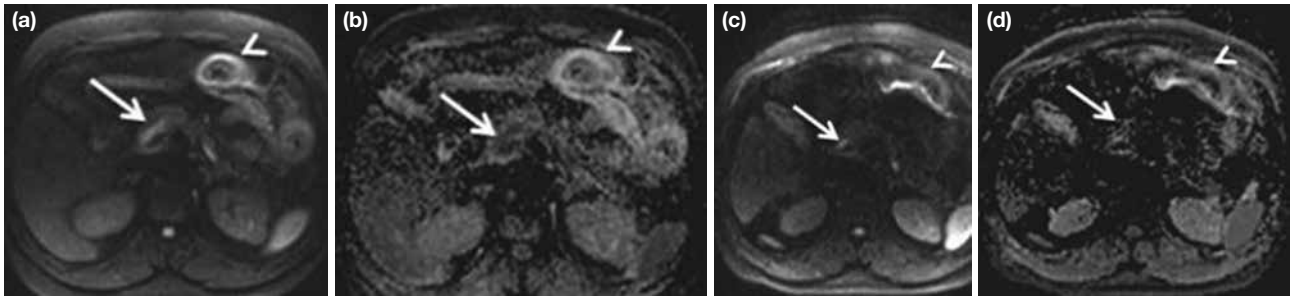

Figure 2. a–d. *A 43-year-old man presenting with abdominal pain, nausea and vomiting. The small bowel ischemia and acute portal vein-superior mesenteric vein thrombus (arrow) shows high signal intensity on axial diffusion-weighted MR image and corresponding low signal intensity on ADC map at presentation* ***(a, b)****. On follow-up axial diffusion-weighted MR images after medical treatment, lysis of portal vein-superior vein thrombus and healing of bowel wall (arrow head) is seen* ***(c, d)****.*

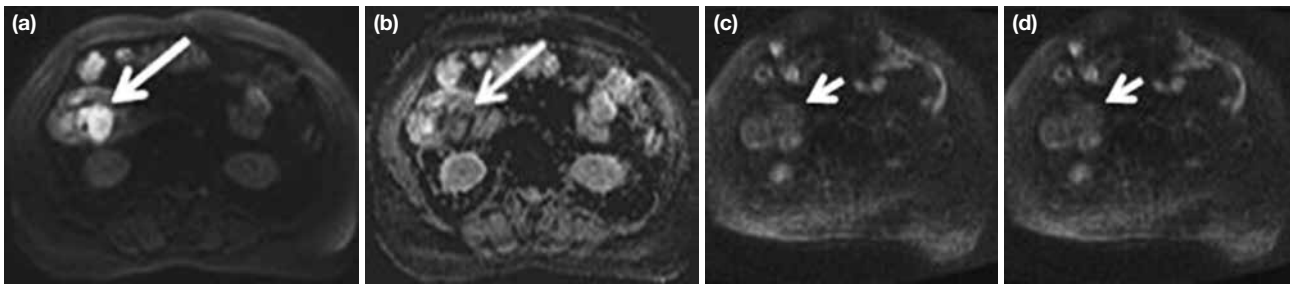

Figure 3. a–d. *A 72-year-old woman presenting with right-sided abdominal pain and leukocytosis (white blood cell count, 16.600/μL [reference value, <10.000/μL]). Initial diffusionweighted MR image and ADC map show pericecal abcess formation (long arrow) due to perforated appendicitis (Plastron appendicitis) that has markedly high signal intensity on diffusion image with corresponding low signal intensity on ADC map* ***(a, b)****. On control diffusion-weighted MR images after medical treatment the abscess has disappeared (short arrow)* ***(c, d)****.*

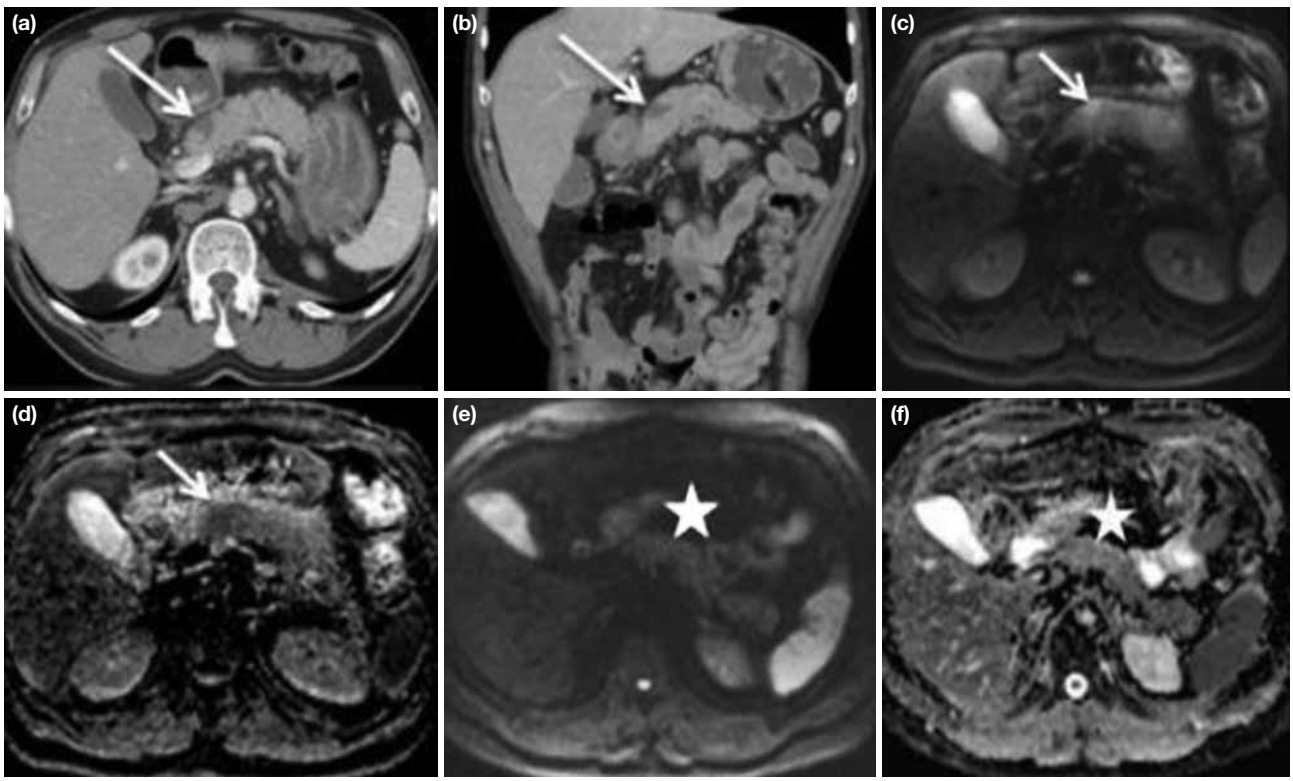

Figure 4. a–f. *Focal pancreatitis in a 55-year-old man. Contrast enhnaced CT shows a focal hipodense area (long arrow) at the body of pancreas compatible with focal pancreatitis* ***(a, b)****. Axial diffusion weighted MR image (b=1000 sec/mm2) shows the focal pancreatitis (short arrow) as a hyperintense area with corresponding hypointensity on axial ADC map (restricted diffusion)* ***(c, d)****. After medical treatment, follow-up diffusion weighted MR images show disappearance of diffuse enlargement of pancreas and focal pancreatitis (star)* ***(e, f)****.*

contrast media. We did not perform statistical analysis of changes in DW-MR and laboratory findings during follow-up period. This issue may be studied in the future with larger patient groups.

On the other hand, repeated MR scanning during follow-up may not be cost effective and practical as in many institutions the MR machine may not be available for 7/24 hours and MR imaging is much more expensive than USG and CT.

In conclusion, we suggest that DW-MR is an efficient and reliable imaging predictor for management and monitoring of medical treatment for various causes of acute abdominal pain. DW-MR does not have ionizing radiation and there is no need of contrast agent. It is clear that DW-MR can prevent unnecessary CT scans, and thus helps to reduce ionizing radiation and complications related to contrast agents.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Hashimoto Tiroiditi Olan Hastalarda Malignensi Tesbitinde İnce İğne Aspirasyon Biyopsisinin Etkinliği

The Credibility of Fine-Needle Aspiration Biopsy for Malignancy in Patients with Hashimoto Diseases

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ABSTRACT

Aim: *This study aimed to research the presence of malignancy in patients with Hashimoto's thyroiditis, and to examine the reliability of preoperative fine-needle aspiration biopsy (FNAB).*

Material and Method: *This retrospective study included 66 patients who were operated on due to nodular goiter between July 2011 and December 2014. The patients underwent thyroidectomy following a cytologic analysis with FNAB. Hashimoto's thyroiditis was testified with histopathology in all patients.*

Results: *FNAB outcome were described as malignant in 13 (19.6%), benign in 21 (31.8%), inadequate in 7 (10.6%), and suspicion for malignancy in 25 (37.8%) cases. After thyroidectomy, existence of papillary thyroid carcinoma and follicular variant of papillary thyroid carcinoma were found in 14 (21.2%) and 2 (3.0%) patients, respectively. With regard to malignancy, FNAB displayed a specificity of 39%; sensitivity of 79%; false negative ratio of 13.9%; false positive ratio of 70.1%; positive predictive value of 32.1%; diagnostic accuracy of 51%; and negative predictive value of 86.0%.*

Conclusion: *This coexistence of Hashimoto's thyroiditis and papillary thyroid carcinoma is fairly mutual. FNAB outcome for such cases are difficult to score, and they are probably to rise the number of false positive cases.*

Key words: *malignancy; fine needle aspiration biopsy; Hashimoto's thyroiditis; cytopathology; histopathology*

ÖZET

Amaç: *Bu çalışmanın amacı Hashimoto tiroiditli hastalarda malignite varlığını analiz etmek ve preoperatif ince iğne aspirasyon biyopsisinin (İİAB) güvenirliliğini değerlendirmektir.*

Materyal ve Metot: *Bu retrospektif çalışmaya Temmuz 2011 ile Aralık 2014 arasında nodüler guatr nedeniyle opere edilen 66 hasta dahil edildi. Bu hastalarda preoperatif İİAB ile sitopatolojik değerlendirme ve sonrasında tiroidektomi operasyonu yapıldı. Tüm hastalara histopatolojik değerlendirme ile Hashimoto tiroiditi kesin tanısı koyuldu.*

Bulgular: *İİAB sonuçları olguların 21'inde (%31,8) benign, 25'inde (%37,8) malignite için şüpheli, 13'ünde (%19,6) malign ve 7'sinde (%10,6) yetersiz olarak yorumlandı. Tiroidektomi sonrasında 14 hastada (%21,2) ve 2 hastada (%3,0) sırasıyla tiroid papiller karsinomu ve tiroid papiller karsinomunun folliküler varyantı saptandı. Malignite saptama açısından İİAB sonuçlarının duyarlılığı %79, özgüllüğü %39, yalancı pozitifliği %70,1, yalancı negatifliği %13,9, pozitif öngörü değeri %32,1, negatif öngörü değeri %86,0 ve tanısal doğruluk oranı %51 olarak yorumlandı.*

Sonuç: *Hashimoto tiroidi ile papiller tiroid karsinomunun birlikte bulunması sıktır. Hashimoto tiroiditi hastalarında İİAB sonuçlarını değerlendirmek çok güç olup yalancı pozitiflik oranının artması muhtemeldir.*

Anahtar kelimeler: *malignite; ince iğne aspirasyon biyopsisi; Hashimoto tiroiditi; sitopatoloji; histopatoloji*

Giriş

Hashimoto Tiroiditi (HT); kronik lenfositik tiroidit olarak da bilinir. Yaygınlığı %1–4 arasındadır ve yıllık insidansı 10,000 kişide 3–6'dır[1]. Endemik guatrdan sonra tiroid hastalıklarının ikincien sık olanıdır, kadınlarda daha sıktır[2]. Genelde diffüz guatr şeklindedir, çok nadiren bir veya iki nodül baskın olabilir. Preoperatif dönemde bu nodüllerin HT veya HT ilişkili maligniteye bağlı olup olmadığını belirlemek çok zordur. Birçok çalışmada HT ile tiroid neoplazileri arasında güçlü ilişki tespit edilmiş ve HT'nin tiroid malignitesi sıklık oranını yükselttiği bildirilmiştir[3]. Pradeep ve ark.[4] ise serilerinde HT ile ilişkili herhangi bir malignite olgusu saptanmadığını bildirmiştir. İnce İğne Aspirasyon Biyopsisi (İİAB) güvenli bir prosedür olup tiroid hastalıklarında etkinliği iyi tanımlanmıştır[5].

İİAB'in ilk amacı ameliyat gerektiren tiroid nodüllerini saptamak olup benign nodüle sahip hastalarda tiroidektominin genel insidansını azaltmaktır[6,7]. HT

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hastalarında tanı koymada antikor testlerine göre İİAB daha üstün ve uygun maliyetli olarak bildirilmiştir[8]. Yine de yöntemin yalancı pozitif ve yalancı negatiflik oranları diagnostik olumsuzluklara yol açmaktadır[9].

Bu çalışmanın amacı; HT hastalarında malignite varlığını analiz etmek olup, pre-op sitopatolojik ve post-op histopatolojik sonuçları karşılaştırmak suretiyle İİAB'nin güvenilirliğini araştırmaktır.

Materyal ve Metot

Bu retrospektif çalışmaya, Temmuz 2011 ve Aralık 2014 arasında nodüler guatr nedeniyle opere olup HT tanısı koyulan 66 hasta dahil edildi. Hastalara İİAB yapıldıktan sonra tiroidektomi yapıldı. Ameliyat endikasyonları; malignite şüphesi, malign nodüller, USG'de şüpheli malign nodül saptanması, birçok semptomun bir arada bulunması ve kozmetik sebeplerdi. Bütün hastalara, tiroidektomi spesmenlerinin histopatolojik incelemeleri sonucunda HT kesin tanısı koyuldu.

Bir hastada 1 cm'den büyük tiroid nodülü saptanması ve malignite şüphesi olması durumunda USG eşliğinde İİAB yapıldı. USG'de nodülde mikrokalsifikasyon, belirsiz sınırlar ve belirgin hipoekojenite sebebiyle nodül malignite yönünden şüpheli olarak değerlendirildi. İİAB inceleme sonuçlarında; hücresel özellikler; pleomorfizm, nükleus/sitoplazma oranında artış, nükleer oyuklanma (grooving), nükleer inklüzyon, nekroz ve lenfositik infiltrasyonu içeriyordu. Histopatolojik olarak ise belirgin parankim hasarına yol açmış ve kısmen lenfoid folikül yapıları da teşkil eden yoğun lenfositik karakterli inflamatuar reaksiyon izlenmektedir. Folikülleri döşeyen epitel hücrelerinde belirgin sitoplazmik eozinofili ile karakterize Hurthle hücre değişiklikleri dikkati çekmekteydi.

İİAB sonuçlarına göre olgular; benign, malignite şüpheli, malign ve yetersiz materyal olarak sınıflandırıldı. Yeterli İİAB örneği en az 1–2 preparatta en az 10 folliküler epitel parçalarını içermek olarak tanımlandı. İİAB de malignite şüpheli ve malign olan olgulara, USG de şüpheli nodülleri olanlara, birçok semptomun bir arada bulunduğu hastalara ve kozmetik nedenleri bulunan hastalara Bilateral total tiroidektomi operasyonu uygulandı.

Tiroidektomi spesmenlerinin histopatolojik incelemesinde, tiroid folikül destrüksiyonu, germinal lenfositik infiltrasyon varlığı ve fibrotik alanların varlığı, Hurthle hücre metaplazisi, epitel hiperplazisi kronik lenfositik tiroidit (HT) olarak kabul edildi. Ayrıca tiroid dokusunda bulunan diğer benign ve malign lezyonlar kaydedildi. İİAB'nin duyarlılık, özgüllük, pozitif öngörü ve negatif öngörü değerleri ölçülürken şüpheli malignite olguları malignite grubuna katıldı ve yetersiz olanlar çalışmadan çıkarıldı.

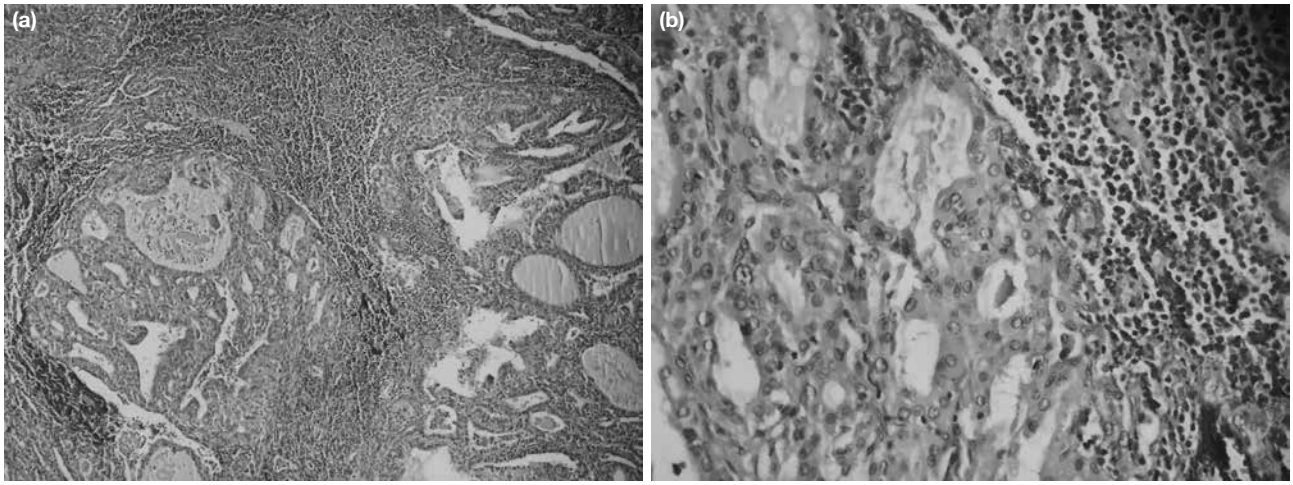
SPSS 15,0 veri analizi için kullanıldı. Kantitatif veriler ortalama standart sapma olarak gösterildi. Tanımlayıcı analizler de yapıldı. Kalitatif verileri karşılaştırmak için ki-kare testi kullanıldı. $p < 0,05$ değeri, anlamlı olarak kabul edildi.

Bulgular

Hastalar, 58 (%87,8) kadın ve 8 (%12,2) erkekten oluşuyordu. Yaş ortalaması 44,3±13,1 yıl (20–79) idi. Üç (%4,5) hastada hipotiroidizm, 2 (%3,0) hastada hipertirodizm ve geri kalan 60 (%90,9) hastada ise ötiroidi mevcuttu. Nodüllerin ortalama çapı 25,6±18,1 mm (13–85 mm aralığında) idi. İİAB sonuçlarına göre; 21 (%31,8) hasta benign, 25 (%37,8) hasta malignite şüpheli, 13 (%19,6) hasta malign ve 7 (%10,6) hasta yetersiz olarak değerlendirildi. Malignite şüphesi ve malignite nedeniyle 38 (%57,5) hastada, USG şüpheli nodül saptanması nedeniyle 15 (%22,7) hastada ve çoklu semptom varlığı ve kozmetik nedenlerle diğer 13 (%19,6) hastada total tiroidektomi operasyonu uygulandı. Tiroidektomi spesmenlerinin histopatolojik incelemesinde tüm hastalarda kesin HT tanısı konuldu (Şekil 1). Ayrıca aynı zamanda 14 (%22,7) hastada papiller tiroid karsinomu, 2 hastada (%3,0) tiroid papiller karsinomu folliküler varyant, 7 (%10,6) hastada folliküler adenom ve 2 (%3,0) hastada Hurthle hücreli karsinom saptandı. Tiroidektomi spesmenlerinin histopatolojik değerlendirme sonuçları ile İİAB sonuçları (Tablo 1, Şekil 2) –HT zemininde malignite açısından– karşılaştırıldı. Histopatolojik değerlendirme altın standart olarak kabul edildiğinde İİAB'nin HT zemininde malignite saptama konusunda duyarlılığı %79, özgüllüğü %39 bulundu. Ayrıca, yalancı pozitiflik oranı %70,1 yalancı negatiflik oranı %13,9, pozitif öngörü değeri %32,1, negatif öngörü değeri %86,0 ve tanısal doğruluk oranı %51 bulundu.

Tartışma

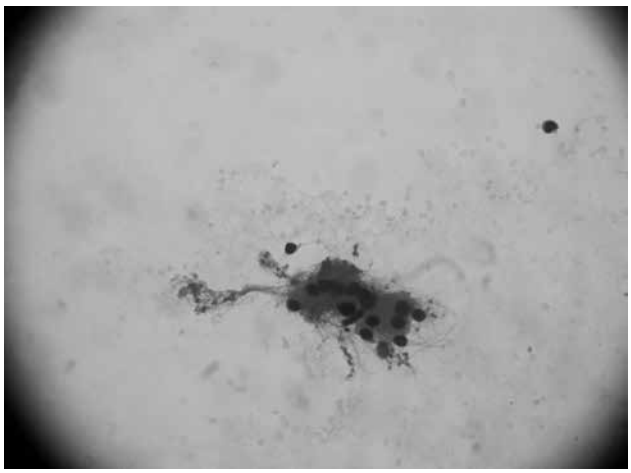
HT, çoğunlukla 4. dekattaki kadınları etkileyen bir otoimmün tiroidit türüdür[1]. Ömür boyu tiroid hormonu replasmanına ihtiyaç duyacak kadar hipotiroidizme yol açabilir[2]. Serimizdeki hastaların ortalama yaşı 44,9 ve kadın/erkek oranı 7,25:1 idi. Hastalarımızın çoğu ötiroidikti ve herhangi bir ilaç tedavisi almamışlardı.



Şekil 1. a, b. *Örneklerde belirgin parankim hasarına yol açmış ve kısmen lenfoid folikül yapıları da teşkil eden yoğun lenfositik karakterli inflamatuar reaksiyon izlenmektedir* ***(a)****. Büyük büyütmede daha net görüldüğü üzere folikülleri döşeyen epitel hücrelerinde belirgin sitoplazmik eozinofili ile karakterize Hurthle hücre değişiklikleri dikkati çekmektedir* ***(b)****.*

Tablo 1. *Histopatolojik tanı ile İİAB sonuçlarının korelasyonu*

	Histopatolojik Tanı		
İİAB	Benign (n, %)	Malign (n, %)	Total (n, %)
Benign	18 (27,2)	3 (4,5)	21 (31,8)
Malignite şüpheli	21 (31,8)	4 (6,0)	25 (37,8)
Malign	6 (9,0)	7 (10,6)	13 (19,6)
Yetersiz materyal	5 (7,5)	2 (3,0)	7 (10,6)
Total	50 (75,7)	16 (24,2)	66 (100)



Şekil 2. *Resimde yer alan bir grup tirositte; hafifçe eksantrik yerleşimli veziküler nükleuslar ve geniş sitoplazmaları ile karakterli Hurtle hücre değişiklikleri dikkati çekmektedir.*

Yalnızca 3 (%4,5) hastada hipotiroidizm vardı. Pradeep ve ark[4]'nın çalışmasında hipotiroidizm oranı %14,3 tü ve çoğu hastaları bizdeki gibi (%90,9) ötiroidikti, bu bulgunun sebebi fokal tiroidite bağlı olabilir.

Çalışmalar gösterdi ki olguların %60–80'inde antitiroglobulin ve antimikrozomal antikorlar pozitiftir ve antikor pozitif olan %10–15 hastada tiroid hastalığı olmayabilir. HT'nin asıl sıklık oranı yalnızca serolojik testlerle saptanandan daha yüksektir. Bu nedenle HT tanısında sitopatolojik değerlendirmenin desteği olmalıdır[2].

HT ile tiroid papiller karsinomunun (TPK) birlikteliği dikkate değer ve tartışılan bir meseledir. Bu birlikteliğin sıklığı %0,3 ile 58 arasında rapor edilmiştir[10–12]. Birinin diğerini tetikleyip tetiklemediği sorusu henüz çözülmemiştir[10]. Konu ile ilgili çalışmalarda çeşitli hipotezler ortaya koyulmuştur. Bir çalışmada[13] tiroiditteki hipotiroidizmde artan TSH'ın foliküler epitel hücre proliferasyonunu artırması sebebiyle tiroid papiller karsinomuna yol açabileceği savunulmuştur. Buna karşın lenfositik infiltrasyon ve tiroidit gelişiminin tümör tarafından salgılanan antijenik materyal tarafından tetiklendiğini savunan çalışmalar da mevcuttur[14,15]. Tiroid dokularının lokal foliküllerinde bulunan lenfositler ve antikorlar sıklıkla HT'ye bağlanmıştır[13,14]. Aynı zamanda foliküllerde bulunan eozinofillerin lenfositlerin agregasyonu için kemotaktik rol oynadığı rapor edilmiştir[15]. Yapılan iki çalışmada TPK hastalarında HT'nin sıklık oranı sırasıyla %28,7 ve %27,3 olarak bildirilmiştir[10,16]. Ancak bu oranı sırasıyla %17,0 ve %20,3 olarak bildiren çalışmalar da mevcuttur[17,18]. Ayrıca Anıl C ve ark.[19] HT hastalarında malignite oranını İİAB sonrasında %1 ve kontrol grubunda %2,7

olarak bildirmiştir. Bu araştırmacılar HT'nin maligniteyi artırmadığını savunmuştur.

Bizim serimizdeki olgularda HT ile TPK'nin birliktelik oranı %25 olarak ortaya koyuldu. Bu hastaların 14'ünde klasik TPK diğer 2 olguda ise TPK folliküler varyant bulunuyordu.

Sitopatolojik ve histopatolojik değerlendirme, HT tanısı için altın standart olarak kabul edilmektedir[9]. İİAB, tiroid lezyonlarını incelemek için ilk basamak metottur[7]. HT'nin sitopatolojik özellikleri arasında, folliküllerin destrüksiyonu, Hurthle hücre metaplazisi, kolloid ve lenfositik infiltrasyon ve epitel hücre birikintileri, fibrozis sayılabilir[1].

HT tanısında İİAB'nin kullanımında çeşitli zorluklar bulunmaktadır. Hiperplazi ve bol kolloid varlığını gösteren sitolojik örneklerde HT tanısı atlanabilir[1]. Ayrıca yarıçapı 3 cm ve daha büyük olan nodüllerde İİAB'nin duyarlılığı düşüktür[19]. HT varlığında, nükleer genişleme, agregasyon, intranükleer inklüzyon ve atipik bulguların (fibrozis, lenfositik infiltrasyon, hurthle hücre metaplazisi) varlığı TPK ile karıştırılmaya yol açabilir ve yanlış tanıya sebep olabilir[20,21].

HT zemininde folliküler neoplazm tanısını koymak için İİAB yapılması genelde yetersiz kalabilir. Çünkü HT, folliküler neoplazmlarda oluşan metaplastik onkositik epitel ve foliküler hücre diferansiasyonu gibi sitolojik değişikliklere yol açabilir. Genellikle adenomu normal tiroid dokusundan ayıran bir kapsül vardır. Kolloid içeren iyi gelişmiş foliküllerden solid ya da trabeküler büyüme paternine kadar değişen morfolojik görünümler de olabilir.

Tiroid lezyonlarında tanısal çalışmada İİAB duyarlılığı, özgüllüğü ve tanısal uygunluğu oranları sırasıyla %65–99, %72–100, ve %53–98 olarak rapor edilmiştir[22–26]. Bazı çalışmalarda HT tanısında İİAB'nin tanısal uygunluğu %92 olarak gösterilmiştir[2,9]. TPK tanısında İİAB'nin duyarlılığı ve özgüllüğü sırasıyla %92 ve %97 olarak bildirilmiştir[27]. Cap ve ark.[6] ise tiroid malignitesi tanısında İİAB için %86 duyarlılık, %74 özgüllük, %75 tanısal uygunluk, %34 pozitif öngörü değeri ve %97 negatif öngörü değeri bildirmiştir. Diğer bir çalışmada duyarlılık %92,6, özgüllük %91,6, tanısal uygunluk %91,9, pozitif öngörü değeri 83,3 ve negatif öngörü değeri %96,5 bulunmuştur[21]. Burch ve ark.[26] ise İİAB'nde yalancı negatiflik oranını %10,3 olarak bildirmiştir.

Bizim çalışmamızın amacı literatürdeki ilgili yayınlardan farklı olarak HT zemininde gelişen TPK olgularında veya HT ve TPK birlikteliğinde İİAB'nin tanısal uygunluk oranını analiz etmektir. Çalışmamızda İİAB'nin sonuçlarında %79 duyarlılık, %39 özgüllük, %70,1 yalancı pozitiflik, %13,9 yalancı negatiflik, %32,1 pozitif öngörü değeri, %86,0 negatif öngörü değeri ve %51 tanısal doğruluk bulundu. Bu sonuçlar ile benign ve malign tiroid lezyonlarından çıkan sonuçlar arasındaki farkın atipik sitolojik değişikliklerden kaynaklandığına inanıyoruz. Bu değişiklikler İİAB sonuçlarının yanlışlıkla şüpheli malignite olarak değerlendirilmesine yol açabilir. Yalancı pozitif sonuçlar da gereksiz ameliyata sebep olabilir. Malignite için şüpheli kabul edilen olgular serinin %38,6'sını oluşturuyordu. Buna göre serolojik olarak HT tanısı konulan olgularda sitopatolojik değerlendirme zorluğundan dolayı tek başına İİAB'nin kullanılması malignite tesbit oranlarının düşmesine yol açabilir.

Tiroid nodüllerinin ameliyat öncesi değerlendirilmesinde İİAB'nin altın standart olarak belirtilmesine karşın çalışmamızdan elde edilen veriler operasyon gerekliliğinin belirlenmesi ve malignensinin ispatında tek başına İİAB'nin etkinliğini desteklememektedir. HT ve TPK birlikteliği sıktır. Bununla birlikte, HT olgularında İİAB'de malignite yönünden yalancı pozitiflik oranını artırma ihtimali olan lenfosittik infiltrasyon ve atipik sitopatolojik değişikliklerin varlığı İİAB sonuçlarının sağlıklı değerlendirilmesini güçleştirmektedir.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

An Analysis of Metacognitive Learning Strategies of Physician Candidates in Terms of Some Variables

Hekim Adaylarının Bilişötesi Öğrenme Stratejilerinin Bazı Değişkenler Açısından İncelenmesi

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ABSTRACT

The aim of this research is determining the metacognitive learning strategies of the 1st, 2nd and 3rd year students (N=614) of Hacettepe University's Faculty of Medicine and analyzing these strategies in terms of different variables. It can be argued in general that in accordance with the collected data they are good at the "Organization" and "Observation" sub-dimensions in terms of knowledge and awareness of the information processing process and they are on an intermediate level in the other two sub-dimensions called "Evaluation" and "Planning". The findings presented with this research show that there is a significant difference regarding gender, academic success and class levels variable on sub-dimensions of metacognitive learning strategies.

Key words: *metacognitive learning strategies; physician candidates; academic success; learning*

ÖZET

Bu araştırmanın amacı, Hacettepe Üniversitesi Tıp Fakültesinde birinci, ikinci ve üçüncü sınıflarda öğrenim gören öğrencilerin (N=614) bilişötesi öğrenme strateji düzeylerini belirleyerek, bu stratejileri çeşitli değişkenler açısından incelemektir. Genel olarak elde edilen veriler doğrultusunda hekim adaylarının bilgiyi işleme süreci hakkındaki bilgisinin ve farkındalıklarının "örgütleme" ve "denetleme" alt boyutlarında iyi, diğer iki alt boyut olan "Değerlendirme" ve "Planlama"da ise orta düzeyde olduğu söylenebilir. Ulaşılan diğer sonuçlar hekim adaylarının bilişötesi öğrenme stratejilerinin cinsiyet, akademik başarı ve sınıf düzeyi değişkenlerine göre alt boyutlarda anlamlı farklılıklar olduğunu göstermektedir.

Anahtar kelimeler: *bilişötesi öğrenme stratejileri; hekim adayları; akademik başarı; öğrenme*

Introduction

Learning is basically a process of permanent changes in behaviors where an individual efficiently and consciously gets new knowledge from the environment and integrates it with information already stored in memory through several strategies[1]. In this process external and internal factors play an important role. External factors can be defined as the contextual features where learning takes place, and internal factors are the strategies used by individuals in the learning process[2].

Orienting towards the cognitive theories of behavioral theories brought attention to learning strategies[3]. In brief, learning strategies are ways for individuals to be self-directed and to develop autonomous and independents skills for this purpose[2]. When the literature is examined, it is seen that learning strategies concentrate generally in two categories (cognitive learning strategies and metacognitive strategies). The metacognitive concept, also defined as thinking about thinking and described as "individuals'knowledge of the self-cognitive system and structure"[4].

In metacognitive learning strategies there are three groups of strategies[5]. These are centering, planning and evaluation. In the questionnaire called "Motivation and Strategies of Learning Questionnaire (MSLQ)" were divided learning strategies into nine sub-dimensions without differentiating cognitive and metacognitive strategies[6]. These are explanation, analysis, organization, critical thinking, metacognition, time management, learning from peers of the same age and cooperation.

As mentioned above it was assessed that students with high metacognitive learning strategies were

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better in problem solving and they learned easily. However when the literature was examined, it was determined that there was no study indicating the relationship between physician candidates'metacognitive learning strategies and their academic success. In this context the aim of this research is determining the metacognitive learning strategies of the 1st, 2nd and 3rd year students of Hacettepe University's Faculty of Medicine and analyzing these strategies in terms of different variables:

1. Which cognitive learning strategies do physician-candidates use?
2. Is there a meaningful difference in the metacognitive learning strategies that physician-candidates use according to classes and genders?
3. Is there a meaningful difference in the learning strategies that physician-candidates use according to their academic success?

Material and Method

Research Model

The survey method is used in this research. The survey model is a research approach aiming to define a present situation as it is[7].

Study Group

The study group consists of freshman, junior and senior physician candidates of the 2014–2015 academic year in Hacettepe University's Faculty of Medicine (N=614). 51.5% of students were female and 48.5% of them were male who participated in study.

Data Collection Tools

In this research, the "Bilişötesi Öğrenme Stratejileri Ölçeği (BÖSÖ) [Metacognitive Learning Strategies Scale]" developed by Namlu (2004) was used for examining metacognitive learning strategies of physician-candidates. BÖSÖ consists of 4 factors and 21 questions. In the scale including Never (1), Sometimes (2), Often (3) and Always (4) choices, the first, second and fifth questions were graded in reverse order. The lowest score to be obtained from the scale was 21 and the highest score was 84. The lowest score for the sub-dimensions of the scale called "planning strategies" and "organization strategies" was 6 and the highest score was 30; the lowest score for "observation strategies" was 5 and the highest score was 25; the lowest score for "evaluation strategies" was 4 and the highest score was 20. For the validity and credibility of the scale, normal distribution analyses, factor analyses, internal consistency coefficients, item-total correlation coefficients and distinctive validity analyses were conducted. The university students who participated in the research numbered 655. Structure validity results indicated that the scale has four factors explaining the total% 45 of variance. For example, the Cronbach Alpha coefficient was .82 for the whole scale .69 for "planning strategies", .74 for "organization strategies", .67 for "observations strategies", and .48 for "evaluation strategies". As a result of all analyses, it was assessed that the scale was valid and credible in measuring the metacognitive learning strategies of university students. In this research, the Cronbach Alpha coefficient was .76 for the whole scale .63 for "planning strategies", .71 for "organization strategies", .64 for "observation strategies", and .42 for "evaluation strategies".

Data Analysis

For the statistical analysis of the collected data for the research, the Statistical Package for the Social Sciences (SPSS) 18 package program was used. For the normality assumption test of the data obtained in BÖSÖ, the Shapiro-Wilks Normality Test was used. As a result of this test, it was determined that the data showed a normal distribution. Therefore the t test from the parametric tests and Anova test methods were used in data analysis. For the significance test, .05 level was administered.

Results

Metacognitive Learning Strategies of Physician-Candidates

In accordance with the first sub-problem of the research, descriptive statistics related to the metacognitive learning strategies scores of physician-candidates are indicated in Table 1.

In accordance with the collected data they are good at the "organization" and "observation" sub-dimensions in terms of knowledge and awareness of the information processing process and they are on an intermediate level in the other two sub-dimensions called "Evaluation" and "Planning".

Changes in Physician-Candidates' Scores Related to Metacognitive Learning Strategies According to Genders

The Levene test was applied to determine whether the scores related to metacognitive learning strategies of physician-candidates differ according to genders or not and scale distribution came out to be homogenous ($p > 0.05$). In accordance with this, the t test was applied to independent groups to determine if the difference among the average scores in terms of the gender variable is significant or not.

In Table 2, total scores obtained from all dimensions are indicated to be 58.95 for females and 58.01 for males according to views of physician-candidates. According to t-test results applied to determine if the difference is statistically significant, physician-candidates'scores of metacognitive learning strategies in terms of the gender variable showed significant differences in sub-dimensions. When sub-dimensions were examined, in "organizations strategies" and "observation strategies" dimensions the difference came out to be significant in favor of females.

Changes in Physician-Candidates' Scores Related to Metacognitive Learning Strategies According to Class Levels

In Table 3, it is seen that physician-candidates'average scores of metacognitive learning strategies indicate differences according to class levels. To determine if this difference is statistically significant the Levene test was applied and it was assessed that the distribution was homogenous ($p > 0.05$) in the whole scale and sub-scales. In accordance with this, to determine if the difference among the average scores is significant or not,

Table 1. *Values related to the scores of physician-candidates in the metacognitive learning strategies*

Dimensions	Number of questions	Lowest score	Highest score	$\bar{x}$	Sd	$\bar{x}$/k
Planning strategies	6	6.00	24.00	14.79	1.88	1.94
Organization strategies	6	6.00	24.00	16.50	2.30	3.34
Observation strategies	5	5.00	20.00	17.64	2.81	2.83
Evaluation strategies	4	4.00	16.00	9.54	2.03	2.02
Whole scale	21	21.00	84.00	58.49	7.15	2.78

Table 2. *T-test results of physician-candidates'scores of metacognitive learning strategies according to the gender variable*

Gender	N	Metacognitive learning strategies	$\bar{x}$	sd	T	p
Female	316	Planning strategies	14.72		1.00	0.315
Male	298		14.88			
Female	316	Organization strategies	16.86		2.80	0.005*
Male	298		16.11			
Female	316	Observation strategies	17.91	612	2.44	0.015*
Male	298		17.36			
Female	316	Evaluation strategies	9.44		1.30	0.193
Male	298		9.65			
Female	316	Whole scale	58.95		1.62	0.104
Male	298		58.01			

Table 3. *Values of physician-candidates'scores of metacognitive learning strategies in terms of Class Levels*

	1. Class			2. Class			3. Class		
Dimensions	N	$\bar{x}$	sd	N	$\bar{x}$	sd	N	$\bar{x}$	sd
Planning strategies	151	14.99	2.31	267	14.60	1.74	196	14.91	1.94
Organization strategies		18.18	3.10		15.75	2.96		16.21	3.56
Observation strategies		18.39	2.84		17.36	2.69		17.45	2.91
Evaluation strategies		10.17	1.86		9.15	1.88		9.59	2.21
Whole scale		61.74	7.38		56.88	6.32		58.18	7.26

one way analysis of the variance was conducted. The results are indicated in Table 4.

According to the findings obtained in Table 4, it was assessed that physician-candidates'average scores of metacognitive learning strategies indicate significant differences in class levels sub-dimensions and that it showed significant differences ($p < 0.05$). The reason for this significant difference in metacognitive learning strategies of physician-candidates is that according to Tukey test analysis results, among first-year, second-year and third-year students there is a significant difference in favor of first-year students.

Changes in Physician-Candidates' Scores Related to Metacognitive Learning Strategies According to Academic Success

In accordance with the third problem of the research, the Anova analysis test results, regarding the fact that the average scores of metacognitive learning strategies of physician-candidates in terms of the academic success variable indicate changes in sub-dimensions creating the metacognitive learning strategies, can be seen in Table 5.

Table 4. *The analysis of variance results of physician-candidates'scores of metacognitive learning strategies according to class levels variable*

Dimensions	Class	N	$\bar{x}$	Sd	F	P	Variables with significant differences
Planning strategies	1. Class (A)	151	14.99	2.31	2.505	0.083	
	2. Class (B)	267	14.60	1.74			
	3. Class (C)	196	14.91	1.87			
Organization strategies	1. Class (A)	151	18.18	3.10	28.860	0.000*	A-B, A-C
	2. Class (B)	267	15.75	2.96			
	3. Class (C)	196	16.21	3.56			
Observation strategies	1. Class (A)	151	18.39	2.84	7.048	0.001*	A-B, A-C
	2. Class (B)	267	17.36	2.69			
	3. Class (C)	196	17.45	2.91			
Evaluation strategies	1. Class (A)	151	10.17	1.86	12.728	0.000*	A-B, A-C
	2. Class (B)	267	9.15	1.88			
	3. Class (C)	196	9.59	2.21			
Whole scale	1. Class (A)	151	61.74	7.38	24.209	0.000*	A-B, A-C
	2. Class (B)	267	56.88	6.32			
	3. Class (C)	196	58.18	7.26			

Table 5. *The analysis of variance results of physician-candidates' scores of metacognitive learning strategies according to the academic success variable*

Dimensions	Academic success	N	$\bar{x}$	sd	F	P	Variables with significant differences
Planning strategies	Low (A)	200	14.35	2.18	11.677	0.000*	A-B, A-C, B-C
	Medium (B)	152	14.54	1.96			
	High (C)	139	15.30	1.46			
Organization strategies	Low (A)	200	16.12	3.63	3.631	0.027*	A-B, A-C, B-C
	Medium (B)	152	16.87	3.03			
	High (C)	139	17.12	3.28			
Observation strategies	Low (A)	200	17.47	3.12	3.959	0.020*	A-B, A-C, B-C
	Medium (B)	152	17.71	2.81			
	High (C)	139	18.38	2.45			
Evaluation strategies	Low (A)	200	9.14	2.18	3.976	0.019*	A-B, A-C
	Medium (B)	152	9.67	1.88			
	High (C)	139	9.71	1.79			
Whole scale	Low (A)	200	56.29	8.36	5.344	0.005*	A-B, B-C
	Medium (B)	152	58.05	6.20			
	High (C)	139	59.58	6.07			

When Table 5 is examined, it is indicated that there are significant differences in physician-candidates' metacognitive learning strategies in terms of academic success ($p < 0.05$). In other words, it was determined that overall success levels increase in parallel with adequacy levels in metacognitive learning strategies of physician-candidates. The reason for this significant difference in the success levels of the physician-candidates between students with low academic success levels and medium academic success levels and between students with medium academic success levels and high academic success levels is, according to Tukey HSD test analysis results, due to the metacognitive learning strategies of the physician-candidates.

Discussion

One of the principal purposes of education is providing the significance of the information taught and learned in an educational institution and increasing its connection with real life and schooling students to adopt the idea of life-long learning. The metacognitive learning strategies, which have an important place in the framework of cognitive theory, are basically strategies that enable students to control their cognition and arrange their learning processes using centering, ordering, planning and evaluating functions. It is stated that first these strategies should be known and awareness should be increased in order for individuals to use strategies requiring metacognitive skills at work[8]. From this perspective for a physician to be successful, it is necessary for them to have knowledge regarding their own beliefs and knowledge and skills in order to have comprehensive knowledge of learning and teaching.

The first sub-dimension of metacognitive learning strategies is "organization strategies". These strategies that are to prepare the mind while starting to study suggest that the information needs to be determined in advance according to the metacognitive schemas that exist in the mind. Determining the subjects and key concepts before any learning activity and organization strategies requiring the review of the context to be learned has an important role in metacognitive learning strategies.

The second sub-dimension called "observation strategies" consists of strategies including observation activities focused on the permanent self-learning of a student during a learning activity. It can be stated that these strategies are for checking if a student understands a subject or not, assessing the accuracy of the information in comparison with the previous information, determining information validity and the hierarchical structure of information during learning and enabling self-observation of a student and information observation.

In the third dimension of metacognitive learning strategies, "evaluation strategies" defined as the student's exhibit of learning and following learning skills, exist. In this dimension where a student self-assesses what is learned and to what extent it is learned, strategies including self-testing in terms of information and analyzing unknown information according to test results can be stated to be dominant.

Especially preparing a study plan regarding learning, doing things in time, preparing the right conditions for pre-preparation and mental preparing regarding courses exist under the "planning strategies" sub-dimension.

In this research the aim was to determine metacognitive learning strategies of physician-candidates. The data of 614 out of 1361 students that could be contacted and showed willingness was collected. Of these, 298 (48.5%) are male and 316 (51.5%) are female. Out of the physician candidates, 151 (24.6%) are first-year students, 267 (43.5%) are second-year students and 196 (31.9%) are third-year students.

It can be argued in general that in accordance with the collected data they are good at the "organization" and "observation" sub-dimensions in terms of knowledge and awareness of the information processing process and they are on an intermediate level in the other two sub-dimensions called "Evaluation" and "Planning". It can be considered that their intensive education prevents them from planning and evaluating.

The findings presented with this research show that there is a significant difference regarding the gender variable, in favor of females, in the "organization" and "observation" sub-dimensions of metacognitive learning strategies. This result supports the other findings in literature stating that female students use more learning strategies than male students[9,10,11,12].

According to another finding obtained with this research, metacognitive learning strategies of physician-candidates indicate significant differences in the "organization", "observation" and "evaluation" sub-dimensions in terms of the class levels variable. So it

was determined that this difference is in favor of first-year students in comparison with second and third-year students. This result is pretty shocking. When the literature is reviewed there are findings opposing this finding[11,13,14]. This situation should be remedied by working with bigger examples and by supporting qualitative analyses in detail.

With respect to another finding obtained from this research, metacognitive learning strategies of physician-candidates indicate significant differences in all dimensions in terms of the academic success variable. In other words it was determined that students with higher academic success levels use metacognitive learning strategies more. Studies show that there is a strong relationship between academic motivation, learning strategies adopted by students and their academic success[15,16].

Success and failures of learners enable them to improve their learning strategies. It was assessed in studies made in different subjects and learning levels that academically successful students use learning strategies more in comparison with academically unsuccessful students and that they are more active, aimed and flexible in terms of strategy use[17–21]. This may result from the fact that self-perceptions of successful students are more positive and that they focus more effort on their success. Besides using learning strategies effectively, they have more knowledge of strategies[22,23]. Reviewed studies support the finding suggesting that learning strategies increase academic success on the university level[13,24–27].

As mentioned before, metacognitive information is a factor that facilitates learning. The results of this research indicate that medical education programs should take precautions in terms of improving the metacognitive information of physician-candidates. Suggestions for implementers and researchers developed in accordance with the results of this research are stated below:

The fact that there is a relationship between academic success and metacognitive learning strategies of physician-candidates reveals the necessity for medical education programs to shape these features of physician-candidates for the future. During pre-service educations of physician-candidates, selective courses aiming to improve the level of metacognitive learning strategies use can be included in training programs, and learning activities aiming to increase the use of metacognitive learning strategies in other classes can be arranged.

The needs for metacognitive learning strategies of students with intermediate and low academic success should be met and their developing of new learning strategies and realizing self and effective learning should be supported.

Especially in the third grade where major courses become intensive, the importance of students'strategy use in planning, arranging and evaluating self-learning activities and also in cataloging learning activities should be emphasized. And students should be enabled to arrange learning activities accordingly.

Academic staff/personnel and physician-candidates should be educated in metacognitive learning strategies and students should be enabled to know the structure of their self-cognitive system and how it operates and to use effective strategies. In addition to this, instructors should raise awareness in students in terms of this case.

Research results show that female physician-candidates use metacognitive learning strategies more than male physician-candidates. It can be useful to determine the reasons why male physician-candidates use metacognitive learning strategies less and to give importance to informing them about improving their awareness starting from the first year.

In this research, only the relationships between metacognitive learning strategies used by students, sociodemographic features and academic success were examined. In studies to be conducted in the future, learning strategies of academic staff/personnel and students can be embraced together and they can be exhibited by using education platform variables and data collection techniques.

Finally, in the process of this study, lots of studies on the relationship between metacognitive learning strategies and academic success were encountered. It is thought that future studies will contribute more to this field.

Research can be remade on physician-candidates with a different exampling method to be chosen and the relationship between independent variables and variables that can affect metacognitive learning strategies.

Experimental studies for determining impacts of metacognitive learning strategies on academic success can be performed.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Endoskopik Mide Biyopsisi Sonuçları: Kars İli

Endoscopic Gastric Biopsy Results: Kars Province

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ABSTRACT

Aim: *Today, complaints about the upper gastrointestinal system are frequently encountered among the reasons for referral to health facilities. The most effective method for evaluating these symptoms is endoscopic examination and histopathologic evaluation. In our study, we aimed to evaluate gastric endoscopic biopsy evaluations performed in Kars province histopathologically.*

Material and Method: *Between 2014 and 2016, 1457 patients who applied to our hospital and underwent stomach biopsy were included in the study. Analysis was performed with SPSS 20.0 software package.*

Results: *There were 484 (33.2%) chronic gastritis, 921 (63.2%) active chronic gastritis, 40 (2.7%) invasive adenocarcinomas, 1 (0.1%) intramucosal adenocarcinoma, 1 (0.1%) hyperplastic polyp, 1 (0.1%) villous adenoma and 9 (0.6%) gastric mucosa at morphological limits in the 1457 cases included in our study.*

Conclusion: *We tried to evaluate the frequency of histopathological findings in gastric endoscopic biopsies performed in Kars province in a single center study. We think that our study can shed light on the studies which are going to be done on a larger number of cases.*

Key words: *stomach; endoscopy; prevalence; Kars*

ÖZET

Amaç: *Günümüzde sağlık kuruluşlarına başvuru sebepleri arasında üst gastrointestinal sistemle ilgili şikayetler sıklıkla göze çarpmaktadır. Bu semptomların değerlendirilmesinde en efektif yöntem endoskopik inceleme ve histopatolojik değerlendirmedir. Biz çalışmamızda Kars ilinde yapılan mide endoskopik biyopsi değerlendirmelerini histopatolojik olarak gözden geçirmeyi amaçladık.*

Materyal ve Metot: *2014–2016 yılları arasında hastanemize başvuran ve mide biyopsisi yapılan 1457 olgu çalışmaya alındı. Analizler SPSS 20.0 paket programı ile yapıldı.*

Bulgular: *Çalışmamıza dahil edilen 1457 olgudan 9 (%0,6) olguda morfolojik limitlerde mide mukozası saptanırken 484 (%33,2) olguda kronik, 921 (%63,2) olguda aktif kronik gastrit, 40 olguda (%2,7) invaziv adenokarsinom, 1 (%0,1) olguda intramukozal karsinom, 1 (%0,1) olguda hiperplastik polip ve 1 (%0,1) olguda villöz adenom gözlenmiştir.*

Sonuç: *Kars ilinde yapılan mide endoskopik biyopsilerindeki histopatolojik bulguların sıklığını tek merkezli bir çalışmada değerlendirdik. Çalışmamızın daha geniş olgu sayıları yapılacak çalışmalara ışık tutabileceği düşüncesindeyiz.*

Anahtar kelimeler: *mide; endoskopi; prevalans; Kars*

Giriş

Günümüzde sağlık kuruluşlarına başvuru sebepleri arasında üst gastrointestinal sistemle ilgili şikayetler sıklıkla göze çarpmaktadır. Epigastrik ağrı ve yanma, retrosternal ağrı, bulantı ve kusma başlıca şikayetlerdir. Bu semptomlar bazen fizyolojik nedenler veya farklı hastalıklar nedeniyle olabileceği gibi gastrointestinal sistem (GİS) patolojileri ile birlikte de olabilir[1]. Üst GİS'te benign ve/veya reaktif durumlar yanı sıra malign epiteliyal ya da mezenkimal neoplaziler karşımıza çıkmaktadır. Çeşitli nedenler ile GİS kanserlerinde görülen artışla birlikte, tarama programları önem kazanmış, tüm dünyada olduğu gibi Türkiye'de de endoskopi sayılarında ciddi artışa neden olmuştur[2]. Bu nedenle muayene ve tetkiklerin en kısa sürede yapılması ve semptomları oluşturan patolojinin belirlenmesi önemlidir. Üst GİS'in değerlendirilmesinde en iyi tanı yöntemi endoskopik incelemedir. Endoskopi ile lezyonun tanınması, lezyondan biyopsi alınması ve gerektiği hallerde terapötik girişimlerin uygulanması da mümkün olabilmektedir[3].

Gastrit; zaman içinde klinisyen ile patologlara göre farklı şekilde yorumlanan midenin enflamatuar bir hastalığıdır. Günümüze kadar lokalizasyon, atrofinin ya da pernisyöz aneminin eşlik etmesi, ilaç ya da madde kullanımı gibi çeşitli unsurlara göre sınıflandırma ve isimlendirmeler kullanılmıştır. 1990'da Sydney'de Dünya

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Gastroenteroloji Kongresinden önce gastritlerin derece ve sınıflamasında gastrik biyopsilerin histolojik yorumuna standart bir yaklaşım getirilerek Sydney sınıflama ve derecelendirme sistemi önerildi[4,5]. Gastritlerin Sydney sistemine göre sınıflamasında; morfolojik, etyolojik ve topografik bilgilerin bir şema halinde verilmesi amaçlanmaktadır[4]. Sınıflamada kronik inflamasyon, nötrofil aktivitesi, glandüler atrofi, intestinal metaplazi ve *Helicobacter pylori* (*H.pylori*) yoğunluğu değerlendirilerek derecelendirilme yapılır[4,6].

Mide birçok organ gibi epiteliyal ve mezenkimal tümörleri yanı sıra az sayıda sekonder tümörü bulunan bir organdır. Midede izlenen tümörlerin çoğu epiteliyal nitelikte olup en sık görülen epiteliyal tümör adenokarsinomlardır. Adenokarsinomlar intestinal tip, diffüz tip ve mikst tip olmak üzere Lauren klasifikasyonunda üçe ayrılır. Dünya Sağlık Örgütü Sınıflaması baz alınarak yapılan opsiyonel bir sınıflama da mevcuttur[7].

Biz çalışmamızda, epigastrik ve retrostrenal ağrı, yanma hissi, şişkinlik gibi çeşitli şikayetler ile hastanemize başvuran ve hastanemizde mide endoskopik incelemeleri yapılan olguların histopatolojik bulgularını analiz etmeyi amaçladık.

Materyal ve Metot

Çalışmaya 2014–2016 yılları arasında Kafkas Üniversitesi Sağlık Araştırma ve Uygulama Merkezi Endoskopi Ünitesinde mide biyopsileri alınan 1457 olgu dahil edildi. Olgulara ait biyopsi numaraları Kafkas Üniversitesi Sağlık Araştırma ve Uygulama Merkezi Patoloji Bölümü kayıt defterlerinden belirlenip olgulara ait raporlar hastane bilişim sistemi yardımı ile elde edildi. Rapor değerlendirmelerinden elde edilen sonuçlara olgu yaş ve cinsiyet bilgilerinin eklenmesinden sonra SPSS 20.0 paket programı ile frekans analizleri yapıldı.

Bulgular

Çalışmamıza dahil edilen 1457 olgunun 781'i (%53,6) kadın, 676'sı (%46,4) erkektir. Olguların yaşları 4 ile 92 arasında değişmekte olup ortalama 49,66+16,84, medyan değer 49'dur. Biyopsilerin alındığı lokalizasyonlar Tablo 1'de verilmiştir. 108 (%7,4) biyopside klinik lokalizasyon bildirilmemiş olup histolojik olarak da çeşitli nedenlerden ötürü belirlenememiştir. 9 (%0,6) olguda morfolojik limitlerde mide mukozası saptanırken 484 (%33,2) olguda kronik, 921 (%63,2) olguda aktif kronik gastrit, 40 olguda (%2,7) invaziv adenokarsinom, 1 (%0,1) olguda intramukozal karsinom, 1 (%0,1) olguda hiperplastik polip ve 1 (%0,1) olguda villöz adenom gözlenmiştir. İntestinal metaplazi (İM) için yapılan incelemelerde değerlendirme yapılamayan 44 (%3,0) olgu tespit edilirken İM izlenmeyen 1109 (%76,2) olgu, hafif, orta ve şiddetli İM gösteren sırası ile 189 (%13,0), 74 (%5,1) ve 41 (%2,8) olgu bulunmaktadır. Displazi değerlendirmesinde, değerlendirme yapılamayan 45 (%3,1) olgu mevcutken displazi gözlenmeyen 1364 (%93,6) olgu bulunmaktadır. Hafif şiddette düşük dereceli displazi gözlenen 39 (%2,7), orta şiddette displazi gösteren 2 (%0,1), şiddetli diplazi gösteren 7 (%0,5) olgu bulunmaktadır. Biyopsi yüzeyelliği ya da dokunun bloklanma şekli nedeni ile 618 (%42,4) olguda atrofi değerlendirmesi yapılamamıştır. Değerlendirilebilen biyopsilerde 224 (%15,4) olguda hafif, 31 (%2,1) olguda orta ve 3 (%0,2) olguda şiddetli derecede atrofi saptanırken 581 (%39,9) olguda atrofi dikkati çekmemiştir. *H.pylori* varlığı değerlendirilemeyen 61 (%4,2) olgu bulunmaktadır. 202 (%13,9) olguda *H.pylori* izlenmezken 452 (%31,0) olguda hafif, 534 (%36,7) olguda orta şiddette ve 209 (%14,4) olguda şiddetli derecede *H.pylori* varlığı mevcuttur.

Cinsiyete göre displazi, İM, atrofi ve *H.pylori* dağılımları Tablo 2'de verilmiştir.

İnvaziv adenokarsinom gözlenen 40 olgudan 34'ü (%85,0) intestinal tip adenokarsinom, 4'ü (%10,0) taşlı yüzük hücreli komponenti baskın adenokarsinom ve 2'si (%5,0) müsinöz komponenti baskın adenokarsinom niteliğindedir. 40 olgunun yaşları 32 ile 86 arasında değişmekte olup ortalama 63,55±12,172 olup medyan değer 65'tir. Olguların 12 'si (%30) kadın, 18'i (%70) erkektir.

Tablo 1. *Biyopsi alınma yerlerinin dağılımı (Kars, 2016)*

Lokalizasyon	Sayı (n) / yüzde (%)
Antrum	780/53,6
Antrum ve korpus	363/24,9
Korpus	166/11,4
Mide	108/7,4
Kardia	27/1,9
Prepylorik	4/0,4
Kardia ve korpus	3/0,2
Kardia ve antrum	1/0,1
Fundus	1/0,1
Toplam	**1457/100**

Tablo 2. *Patolojik tanıların cinsiyet üzerine dağılımı (Kars, 2016)*

Patolojik tanı	Kadın (n/%)	Erkek (n/%)
Aktif kronik gastrit	516/66,1	405/59,9
Kronik gastrit	246/31,5	238/35,2
Adenokarsinom	12/1,5	28/4,1
Morfolojik limitlerde mide dokusu	6/0,8	3/0,4
Hiperplastik polip	1/0,1	0/0
İntramukozal karsinom	0/0	1/0,1
Villöz adenom	0/0	1/0,1
Displazi		
Yok	745/95,4	619/91,6
Hafif	23/3,0	16/2,3
Orta	1/0,1	1/0,1
Şiddetli	0/0	7/1,0
Değerlendirme yapılamıyor	12/1,5	33/4,9
İntestinal metaplazi		
Yok	620/79,4	489/72,4
Hafif	87/11,1	102/15,1
Orta	44/5,6	30/4,4
Şiddetli	17/2,2	24/3,6
Değerlendirme yapılamıyor	13/1,7	31/4,4
Atrofi		
Yok	314/40,2	267/39,5
Hafif	128/16,4	96/14,2
Orta	17/2,2	14/2,1
Şiddetli	2/0,3	1/0,1
Değerlendirme yapılamıyor	320/40,9	298/44,1
Helicobacter pylori		
Yok	102/13,1	100/14,8
Hafif	246/31,5	206/30,5
Orta	295/37,8	239/35,4
Şiddetli	118/15,1	91/13,5
Değerlendirme yapılamıyor	20/2,6	40/5,8
Toplam	**781/100**	**676/100**

Tablo 3. *Lokalizasyon ve patolojik tanıların gastrit tipleri üzerine dağılımı (Kars, 2016)*

Lokalizasyon ve patolojik tanılar	Kronik gastrit (n/%)	Aktif kronik gastrit (n/%)
Lokalizasyon		
Mide	39/8,1	47/5,1
Antrum	290/59,8	480/52,1
Korpus	49/10,1	112/12,2
Kardia	7/1,4	7/0,8
Prepylorik	2/0,4	4/0,4
Antrum ve korpus	94/19,4	267/29,0
Kardia ve korpus	1/0,2	2/0,2
Kardia ve antrum	0/0	1/0,1
Fundus	2/0,4	1/0,1
Displazi		
Yok	471/97,3	882/95,8
Hafif	8/1,7	31/3,3
Orta	1/0,2	1/0,1
Şiddetli	0/0	5/0,5
Değerlendirilemiyor	4/0,8	2/0,2
İntestinal metaplazi		
Yok	399/82,4	699/75,9
Hafif	55/11,4	134/14,5
Orta	16/3,3	57/6,2
Şiddetli	13/2,7	27/2,9
Değerlendirilemiyor	1/0,1	4/0,4
Atrofi		
Yok	209/43,2	366/39,7
Hafif	58/12,0	166/18,0
Orta	12/2,5	19/2,1
Şiddetli	0/0	3/0,3
Değerlendirilemiyor	205/42,4	367/39,8
Helicobacter pylori		
Yok	118/24,4	78/8,5
Hafif	210/43,4	240/26,1
Orta	124/25,6	408/44,3
Şiddetli	25/5,2	184/20,0
Değerlendirilemiyor	7/1,4	11/1,2
Toplam	**484/100**	**921/100**

Kronik ve aktif kronik gastritlerde enflamasyon şiddeti değerlendirildiğinde kronik gastritlerde 383 (%79,1) olguda hafif, 99 (%52,5) olguda orta ve 2 (%0,4) olguda şiddetli kronik enflamasyon karşımıza çıkmaktadır. Aktif kronik gastrit olgularında 266 biyopside (%28,9) hafif, 490 (%53,2) biyopside orta ve 165 (%17,9) biyopside şiddetli aktif kronik enflamasyon dikkati çekmektedir. Kronik gastrit ve aktif kronik gastrit olgularının lokalizasyon ve patolojik tanılarının dağılımları Tablo 3'te verilmiştir.

Biyopsi alınma sıklığı açısından en fazla biyopsi alınan iki yer olan antrum ve korpus karşılaştırıldığında displazi, İM, atrofi ve *H.pylori* açısından Tablo 4'deki veriler elde edilmiştir.

Tablo 4. *Patolojik tanıların antrum ve korpustan alınan biyopsilerin üzerine dağılımı (Kars, 2016)*

Patolojik tanı	Antrum (n/%)	Korpus (n/%)
Displazi		
Yok	752/96,5	163/98,2
Hafif	15/1,9	1/0,6
Orta	0/0	0/0
Şiddetli	1/0,1	0/0
Değerlendirilemiyor	10/1,3	2/1,2
İntestinal metaplazi		
Yok	606/77,9	145/87,3
Hafif	99/12,7	13/7,8
Orta	45/5,8	1/0,6
Şiddetli	21/2,7	4/2,4
Değerlendirilemiyor	8/1,0	3/1,8
Atrofi		
Yok	275/35,3	108/65,5
Hafif	104/13,4	11/6,7
Orta	19/2,4	4/2,4
Şiddetli	2/0,3	0/0
Değerlendirilemiyor	379/48,7	42/25,5
Helicobacter pylori		
Yok	128/16,5	23/13,9
Hafif	231/29,7	46/27,7
Orta	277/35,6	68/41,0
Şiddetli	126/16,2	25/15,1
Değerlendirilemiyor	16/2,1	4/2,4
Toplam	**778/100**	**166/100**

Tartışma

Endoskopik inceleme ve histopatolojik değerlendirme, günümüzde üst GİS hastalıklarında olguların kesin tanısını koyduran ve tedavi planlamasına yol gösteren önemli yaklaşımlardır. Klinisyenler endoskopi sırasında makroskopik olarak renk değişikliği, ülserasyon, erozyon gibi çeşitli bulguları tespit ettikleri lokalizasyonlardan biyopsi almanın yanı sıra ailesinde neoplazi öyküsü olan olgularda tamamen normal görünümlü dokulardan da örnekleme yapmaktadırlar. Bizim çalışmamızda bölümümüze ulaşan mide dokusuna ait materyallerin çoğunluğunun antrum lokalizasyonuna ait olduğu saptanmıştır. Bu durum klinisyenlerin en çarpıcı mukozal değişiklikleri antrumda görmesi ile açıklanabilir. Yapılan histopatolojik incelemelerde 1457 olgunun yalnızca 9'unda (%0,6) morfolojik limitlerde mide mukozasının saptanması da klinik-histopatoloji uyumunun göstergesi olarak değerlendirilebilir.

Midenin enflamatuar ve neoplastik hastalıkları dünyada ve ülkemizin farklı yörelerinde farklı sıklıklarda karşımıza çıkmaktadır. 2012'de yayınlanan ve Küba'da yapılan çalışmada gastrit oranı %91,6 olarak bildirilmiştir[8]. Biz ise çalışmamızda %96,4 oranında gastrite rastladık. Bu olguların %33,2'si kronik, %63,2'si aktif kronik gastrit niteliğinde gözlenmiştir. Kars iline uzak yerleşimli bölgelerin verileri değerlendirildiğinde Eskişehir'de yapılan bir çalışmada genel gastrit oranı %23 olarak saptanırken Zonguldak ilinde %78, Isparta'da ise çalışmamızdakine benzer bir oran ile %96 olarak saptanmıştır[2,9,10]. Güneydoğu Anadolu bölgesinde yapılan çalışmalarda Diyarbakır'da %13, Şanlıurfa'da ise %59 oranında gastrit gözlenmiştir[11,12]. Demir ve arkadaşlarının Elazığ'da yaptıkları çalışmada gastrit %64,4 oranında bildirilirken yine Elazığ'da 8453 olgunun değerlendirildiği 2014 tarihli çalışmada gastrit sıklığı %39 olarak raporlanmıştır[13,14]. Komşu il olan Erzurum'da ise gastrit oranı %22 olarak bildirilmiştir[15]. Gastrit oranlarının şehirlere göre ciddi farklılıklar göstermesinde beslenme alışkanlıkları, çevresel faktörler ve ilgili bölgelerin genetik farklılıkları rol oynuyor olabilir. Bizim çalışmamızda saptanan yüksek oran ön planda ulaşım koşullarını akla getirmektedir. Coğrafi ve iklimsel şartlar nedeni ile hastalar ancak ciddi ve persistan şikayetleri olduğunda sağlık kuruluşuna başvurma eğilimi göstermektedir. Bu durumun endoskopi yapılan olgulardaki yüksek gastrit oranını açıklayabileceğini düşünmekteyiz.

Gastrik polipler spesifik bulgusu olmaması nedeni ile çoğunlukla endoskopik inceleme sırasında insidental olarak saptanırlar. Komşu ülke Yunanistan'da 1996 yılında yapılan bir çalışmada gastrik polip oranı %1,2 olarak bulunmuştur[16]. Ülkemizde Düzce'de yapılan çalışmada polip oranı %1,8 saptanırken Bayburt'ta bu oran %0,4, Isparta'da %0,8 olarak bildirilmiştir[1,10,17]. Bizim çalışmamızda gastrik polip sıklığı %0,1 olarak gözlenmiştir. Çevre illerden Elazığ'da gastrik polip oranı %0,9 olarak bildirilirken Erzurum'da bu oran %0,3 olarak bulunmuştur[14,15]. Yüksek bir oran göstermeyen gastrik poliplerin çoğu zaman semptomatik olmaması nedeni ile sağlık kuruluşuna başvurmada öncelikli etken olmadığını ve bu nedenle de düşük oranda karşımıza çıktığı düşüncesindeyiz.

Birleşik Krallıkta uzun bir zaman dilimini kapsayan çalışmada mide tümörü oranı %1,5 olarak saptanmıştır[18]. Düzce'de yapılan çalışmada mide tümörü oranı

%1,99, Bayburt'ta %0,5, Isparta'da %1,4 olarak bulunmuştur[1,10,17]. 1999 yılında Erzurum'da mide tümörü %6,5 oranında bildirilmiştir[15]. Diyarbakır'da %2,1, Şanlıurfa'da %2 oranında tespit edilmiştir[11,12]. Yine Şanlıurfa'da 2016 yılında Harran Üniversitesi'nde 7703 olguda yapılan çalışmada mide tümörlü olgu sayısı 108 (%1,4) ve %24'ü kadın olarak saptanmıştır. Aynı çalışmada tümör olgularının 3'ü 50 yaş altında olup, olguların yaş aralığı 42–93 (ort: 68,38) yaş olarak saptanmış, olguların %4,6'sı stromal tümör, %0,9'u nöroendokrin tümör, %0,9'u lenfoma, %93,6'sı ise adenokarsinoma olarak bildirilmiştir[19]. Bayburt'ta yapılan çalışmada bildirilen %0,5 oranının tümünü erkek hastalar oluştururken Sağlık Bakanlığı verilerinde kadınlarda 2006, 2007, 2008 yılı mide tümör oranları sırasıyla %7,6, %8,4, %8, erkeklerde %14,8, %17,2, %18,5 olarak bildirilmiştir[1,20]. Biz çalışmamızda 1457 olgunun 40'ında (%2,7) invaziv tümör saptadık. 40 olgunun yaşları 32 ile 86 arasında değişmekte olup ortalama 63,55±12,172 olup medyan değer 65'tir. Bu olguların tümü adenokarsinom niteliğinde olup 40 olgudan 34'ü (%85,0) intestinal tip adenokarsinom, 4'ü (%10,0) taşlı yüzük hücreli komponenti baskın adenokarsinom ve 2'si (%5,0) müsinöz komponenti baskın adenokarsinom özelliği göstermektedir. Adenokarsinomların cinsiyete göre dağılımına bakıldığında, %30 oranında kadın, %70 oranında erkek olgu dikkati çekmektedir. Kars ilinin mide tümörü oranı ülkemizin batısında kalan illere göre hafif yüksek, güneydoğu illerine benzer ve komşu il Erzurum'a göre düşüktür. Batı illeri ve Kars arasındaki farklılık özellikle beslenme koşulları ve coğrafi değişiklikleri düşündürmektedir. Erzurum ve Kars arasındaki fark ise malignite hastalarının büyük sağlık merkezlerine başvurma eğilimi nedenli çalışmamızda elde ettiğimiz oranın gerçek tümör sıklığını yansıtmaması ile açıklanabilir.

Gastrit ve MALT lenfoma etyolojisinde yer alan *H.pylori* sıklığı ile ilgili Japonya'da 2017 yılında yayınlanan çalışmada gastrik *H.pylori* prevalansı %6,1 saptanmıştır[21]. Ülkemizde 2016 yılında yayınlanan ve Güneydoğu Anadolu'da yapılan bir çalışmada gastrik biyopsi spesmenlerinden hücre kültürü ve PCR yöntemi ile yapılan çalışmada gastrointestinal şikayetleri olan 129 hastanın 84'ünde %65 *H.pylori* tespit edilmiştir[22]. Şanlıurfada 1999 yılında yapılan çalışmada endoskopi grubunda genel *H.pylori* prevalansı %67,9 olarak saptanırken 120 kadın hastanın 84'ünde (%70), 123 erkek hastanın 81'inde (%66) *H.pylori* saptanmıştır[12]. Bursa'da yapılan çalışmada Sydney klasifikasyonu antrum ve korpustan alınan biyopsilere göre değerlendirilmiştir. Bu bağlamda antrumda *H.pylori* olmayan %76,9 olgu, hafif düzeyde olan %13,4 olgu, orta düzeyde olan %7,6 olgu ve şiddetli %2,2 saptanırken korpusta sırası ile %75,3, %16, %6 ve %4 olguda pozitiflik rapor edilmiştir[4]. Bizim çalışmamızda *H.pylori* varlığı değerlendirilemeyen %4,2 olgu mevcuttur. %13,9 olguda *H.pylori* saptanmazken %81,9 olguda *H.pylori* varlığı saptandı. Kadın hastaların %84,3'ünde çeşitli derecelerde *H.pylori* pozitifliği gözlenirken erkek hastalarda %79,4 olarak gözlendi. Antrum ve korpus verileri değerlendirildiğinde ise antrumda *H.pylori* izlenmeyen %16,5 olgu, hafif *H.pylori* pozitifliği gösteren %29,7 olgu, orta ve şiddetli pozitiflik gösteren sırası ile %35,6 ve %16,2 olgu gözlendi. Korpusta ise bu oranlar sırası ile %13,9, %27,7, %41,0 ve %15,1 olarak saptandı. Kars İli'nde oldukça yüksek oranda *H.pylori* pozitifliğinin saptanması sosyoekonomik durum yanı sıra iklim şartları nedenini akla getirmektedir. Zorlu kış koşullarında kullanma sularının özellikle kırsal alanda donması hijyen sorunlarını beraberinde getirmektedir. Şehirleşme ve kırsal nüfusun kentleşmesi ile *H.pylori* pozitifliğinde azalma oluşabileceği öngörülmektedir.

2012 yılında yapılan ve 427 olgunun dahil edildiği çalışmada antrumda atrofi olmayan %30,3 olgu, hafif düzeyde olan %45,8 olgu, orta düzeyde olan %23,1 olgu ve şiddetli %7 saptanırken korpusta bu oranlar sırası ile %30,7, %66, %21,3 ve %2'olarak bildirilmiştir[4]. Bizim çalışmamızda %39,9 olguda atrofi izlenmezken %17,7 olguda değişik derecelerde atrofi mevcuttur. %42,4 olguda çeşitli nedenlerden ötürü atrofi değerlendirmesi yapılamamıştır. Lokalizasyona göre atrofi değerlendirmesinde antrumda %35,5 olguda atrofi saptanmazken bu oran korpusta %65,5 olarak gözlenmiştir. Antrumda hafif, orta ve şiddetli atrofi oranları sırası ile %13,4, %2,4, %0,3 olarak izlenirken korpusta bu oranlar sırası ile %6,7, %2,4 ve %0 olarak izlenmiştir. Atrofi değerlendirmesinde hafif düzeyde yüksek sonuç elde edilmiş olmakla birlikte çeşitli nedenler ile değerlendirilemeyen %42,4 oranındaki biyopsi değerlendirmesi yapılabilseydi sonuçların benzer çalışmalardaki oranlara yaklaşması imkan dahilinde olabilirdi.

Isparta'da yapılan çalışmada 1095 mide endoskopik biyopsi materyali incelemesinde İM %9,68 saptanmıştır. Çalışmadaki 106 İM olgusunun %83,96'sı antrum, %13,20'si korpus ve %2,83'ü kardiada izlenmiştir[10]. 2012 yılında Bursa'da yapılan çalışmada ise antrumda İM olmayan %69,7 olgu, hafif düzeyde olan %17 olgu, orta düzeyde olan %10,1 olgu ve şiddetli %3,2 olgu

saptanırken korpusta bu oranlar sırası ile %70, %12, %16 ve %2 olarak rapor edilmiştir[4]. Bizim çalışmamızda ise %3 olguda değerlendirme yapılamazken %76,2 olguda İM saptanmamıştır. Bütün olguların %20 ,8'inde farklı şiddetlerde İM gözlenmiştir. Antrumda İM gözlenmeyen %77,9, korpusta %87,3 olgu mevcuttur. Hafif şiddetli İM izlenen antrumda %12,7 olgu bulunurken korpusta %7,8 olgu vardır. Orta şiddette İM gösteren antrumda %5,8, korpusta %0,6 olgu, şiddetli İM gösteren antrumda %2,7, korpusta 2,4 olgu gözlenmiştir. İM oranlarında ülke içinde değişiklik olması ön planda beslenme alışkanlıklarını düşündürmektedir. Ayrıca sosyoekonomik ve coğrafi şartların da önem arz ettiği akılda bulundurulmalıdır.

Sonuç olarak biz çalışmamızda Kars ilinde yapılan mide endoskopik biyopsilerindeki histopatolojik bulguların sıklığını belirlemeye çalıştık. Çalışmanın kısıtlılığı tek bir merkezi içermesi olsa da bundan sonra daha geniş olgu sayıları yapılacak çalışmalara ışık tutabileceği düşüncesindeyiz.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Modified FOLFIRI-Bevacizumab Regimen in the Patients with Metastatic Colorectal Cancer Who Had Progressed After Oxaliplatin-Based Regimen

Oksaliplatin-Temelli Rejim Altında Progresyon Gösteren Metastatik Kolorektal Kanserli Hastalarda Modifiye Folfiri-Bevasizumab Rejimi

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ABSTRACT

Aim: *We aimed to investigate the efficacy and tolerability of modified FOLFIRI-Bevacizumab (mFOLFIRI-B) regime in the second-line treatment of metastatic colorectal cancer (mCRC) patients who received oxaliplatin-based regimen in the first-line treatment.*

Material and Method: *The patients treated with mFOLFIRI-B regimen in second-line therapy who had progressed after oxaliplatin-based chemotherapy were included in this study. The datas of toxicity and efficacy of the regimen were retrospectively evaluated.*

Results: *Total 172 mCRC patients had received mFOLFIRI-B regime in the second-line treatment. 39.5% objective response rate, 9.0 months (7.6 to 10.3) median progression-free survival, 19.0 months (15.1 to 26.2) median overall survival were found. Grade 3/4 toxicity was observed in 33.7%. Grade 3/4 hematologic toxicity was most frequently observed toxicity (31.9%).*

Conclusion: *mFOLFIRI-B is an efficient and safe regimen for the second-line treatment of mCRC patients after the oxaliplatin-based regimen.*

Key words: *metastatic colorectal cancer; second-line chemotherapy; modified FOLFIRI-Bevacizumab*

ÖZET

Amaç: *İlk-sıra tedavide oksaliplatin-temelli rejim alan metastatik kolorektal kanserli (mKRK) hastalarda ikinci-sıra tedavide modifiye FOLFIRI-Bevacizumab (mFOLFIRI-B) rejiminin etkinlik ve tolerabilitesi araştırıldı.*

Materyal ve Metot: *Çalışmaya ilk-sıra tedavide oksaliplatin-temelli rejim alan, ardından progresyon gözlenen ve ikinci-sıra tedavide mFOLFIRI-B rejimi alan mKRK'li hastalar alındı. Toksisite ve etkinlik ile ilgili veriler retrospektif olarak değerlendirildi.*

Bulgular: *Toplam 172 mKRK'li hasta ikinci-sıra tedavide mFOLFIRI-B rejimi almıştı. Hastaların %39,5'inde objektif cevap, 9,0 aylık (7,6 ile 10,3 arası) median progresyonsuz yaşam, 19,0 aylık (15,1 ile 26,2 arası) median tüm yaşam saptandı. Grade 3/4 toksisite %33,7 oranında tespit edildi. Grade 3/4 hematolojik toksisite %31,9 oranında tespit edildi.*

Sonuç: *Sonuç olarak mKRK'li hastalarda oksaliplatin-temelli rejim sonrası ikinci-sıra tedavide mFOLFIRI-B rejimi etkili ve güvenilir bir tedavi rejimidir.*

Anahtar kelimeler: *metastatik kolorektal kanser; ikinci-sıra kemoterapi rejimi; modifiye FOLFIRI-Bevacizumab rejimi*

Introduction

Colorectal cancer is a widespread and fatal disease. While constituting approximately 10% of all cancers, it is the third commonest malignancy in both genders and is the third leading cause of death. It is responsible of 10% of deaths due to cancer[1,2]. The main method of therapy in colorectal cancers is surgical therapy. A part of stage II patients and stage III patients are given adjuvant chemotherapy (CT) following surgical treatment. In stage IV patients, the main treatment approach is systemic CT[2–4]. In rectal cancer, adjuvant or neoadjuvant chemoradiotherapy (CRT) is added in addition to these approaches[5].

Metastatic colorectal cancer (mCRC) constitutes an important part of all colorectal cancers[6]. Survival time increases and symptoms related to the disease are controlled with use of CT[7–9]. Currently, survival time has increased to more then 2 years with new generation CT drugs including oxaliplatin and irinotecan and

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with addition of targeted drugs including bevacizumab and cetuximab[10–14]. In addition, survival rates have been shown to increase further with current efficient CT which renders unresectable metastases resectable and with performed of metastasectomy[15–18].

In treatment of mCRC, combination regimens based on 5-FU are still the main therapeutical options. FOLFOX and FOLFIRI regimens which are constituted by adding oxaliptalin and irinotecan to 5-FU and combination regimes formed by adding bevacizumab and cetuximab are the most frequently used regimens[19–23].

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that selectively binds to vascular endothelial growth factor (VEGF) and inhibits its interaction with its receptor[24]. It has been shown that there is considerable advantage of PFS and OS by usage of 5-FU, leucovorin and irinotecan combination regimen in first line therapy of mCRC[13,25–28]. Nowadays, there is suggestion of combination of bevacizumab with 5-FU, leucovorin plus irinotekan or 5-FU, leucovorin plus oxaliplatin in the first-line therapy of mCRC patients[29].

Generally, in patients with K-ras mutant tumor, combination of bevacizumab with FOLFIRI regimen in first line treatment of mCRC have been accepted as standard therapy. However there are very few reports in the literature about efficieny and toxicities of second-line modified FOLFIRI-Bevacizumab (mFOLFIRI-B) regimen in mCRC patients who had progressed after oxaliplatin-based chemotherapies. It has been shown that bevacizumab containing regimen is an effective therapy in first-line treatment of mCRC patients, therefore it seems to be diffucult to use bevacizumab containing regimens as second-line therapy in any prospective study.

For this reason, evaluating of efficieny and tolerability of mFOLFIRI-B regimen as a second-line therapy is an important topic. Thus the aim of our study is showing retrospectively the efficieny and adverse effects of second-line mFOLFIRI-B regimen in mCRC patients who had progressed after oxaliplatin-based chemotherapies.

Material and Method

Patients

Patients with a diagnosis of mCRC who showed progression under the first-line treatment with oxaliplatin-based regime and received mFOLFIRI-B regime as the second-line treatment between January 2004 and August 2013 were evaluated. The files of the patients were evaluated retrospectively and data about the efficiency of CT, toxicities and survival were obtained.

Patients with stage IV colorectal cancer according to American Joint Committee on Cancer's (AJCC) Cancer Staging 6th edition 2002 TNM grading system who showed progression under the first-line treatment with oxaliplatin-based regime in metastatic period and received mFOLFIRI-B regime as the second-line therapy were included in the study[30].

Treatment

mFOLFIRI-B regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2.400 mg/m^2 46-hour infusion + irinotecan 180 mg/m^2 + bevacizumab 5 mg/kg every 14 days. Modified FOLFOX6 regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2400 mg/m^2 as a 46-hour infusion + oxaliplatin 85 mg/m^2 given once in every 14 days. FOLFOX6 regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2400 mg/m^2 as a 46-hour infusion + oxaliplatin 100 mg/m^2 given once in every 14 days. FOLFOX7 regime included folinic acid 400 mg/m^2 + 5-FU 400 mg/m^2 bolus + 5-FU 2.400 mg/m^2 46-hour infusion + oxaliplatin 130 mg/m^2 every 14 days. XELOX4 regime included capecitabine 2000 mg/m^2 given 2 weeks on 1-week off regimen + oxaliplatin 85 mg/m^2 every three weeks. XELOX7 regime included capecitabine 2000 mg/m^2 given 2 weeks on 1-week off regimen + oxaliplatin 130 mg/m^2 every three weeks.

Response Evaluation

Response was evaluated after every 6 cycles or after three months. Evaluation of response was done according to tumor response assessment criteria of the World Health Organization[31]. Accordingly, disappearance of the tumor completely was considered as complete response (CR), regression of the target lesion with a rate of 50% or more was considered as partial response (PR), regression of the target lesion less than 50% or progression of the target lesion less than 25% was considered as stable disease (SD) and progression of 25% or more in the target lesion or observation of a new lesion was considered as progressive disease (PD). The total of CR and PR was evaluated as objective response rate (ORR).

After 6 cycles CT or after three months, 50% or more reduction in serum carcinoembryonic antigen (CEA) level was considered as tumor marker response. Evaluation of toxicity was done according to National Cancer Institute-Common Toxicity Criteria Version 2.0[32].

The time from the beginning of first cycle day 1 of second-line CT to development of progression or death from any reason was considered as progression-free survival (PFS). The time from the first cycle day 1 of second-line CT to last follow-up or death was considered as overall survival (OS).

Statistical analysis of the data was done using Statistical Package for Social Sciences for Windows (SPSS) Version 15.0 software. Independent group ratios were compared using the chi-square test. Kaplan-Meier method was used for analyses of PFS and OS. Two survival curves were compared using Log-rank Test. The statistical significance was considered as $p < 0.05$.

Results

Patient Features

A total of 172 patients were evaluated. The median age of the all patients was 57 (18–81). 71 (41.3%) patients were female and 101 (58.7%) were male. 98 (56.9%) patients had metastatic colon cancer (Table 1). FOLFOX7 as the first-line regimen was the most common received by patients (Table 2). There was no determined relationship between survival time and first-line CT regimen ($p = 0.568$).

The most commonly observed metastatic organ was the liver (Table 1). 63 (36.6%) of the patients had their primary tumor operated before mFOLFIRI-B regimen was started (Table 2).

Treatment Regimens

The median number of cycles for mFOLFIRI-B regimen was 6 (4–18). After mFOLFIRI-B regime 15 (8.7%) patients received fifth-line CT (Table 2).

Efficiency

ORR was obtained in 68 (39.5%) patients, 11 (6.3%) of these had CR and 57 (33.1%) had PR. Median follow-up time was found to be 42 (7–154) months from the time of metastases was detected. Median follow-up time was 16 (7–69) months from the time of beginning of day 1 of second-line treatment. Median PFS was 9.0 (7.6 to 10.3) months, median OS was 19.0 (15.1 to 26.2) months (Figure 1, 2). Serum level of CEA reduction was observed in 35 (20.3%) patients who had a high level of serum CEA. Primary tumor resection was performed in 12 (6.9%) of the patients and metastasectomy was performed in 14 (8.1%) of the patients. Hepatic metastasectomy was most commonly performed (Table 3).

Toxicity

Grade 3/4 toxicity was observed in 58 (33.7%) patients. Hematologic toxicity was the most commonly observed (31.9%). The most common hematologic toxicity was found to be neutropenia (27.9%). Hypertension and proteinuria which are significant side effects of bevacizumab, was found to be 6.4% and 4.0%, respectively (Table 4).

Discussion

Colorectal cancer is the third leading cancer among all cancers. Approximately half of colorectal cancers are metastatic at the time of diagnosis or become metastatic and need treatment subsequently. Currently, median survival has increased to more than two years due to advances in CT drugs used in recent years. Adding of oxaliplatin or irinotecan to combination of 5FU and leucoverin is mostly accepted CT protocol in treatment of mCRC. The another important point is deciding of second-line CT regimen after progression of following first-line therapy in mCRC. It has been realized that by addition of bevacizumab, a monoclonal antibody the CT response rate has increased. Therefore bevacizumab mostly has been used in first-line CT which is critical point. But especially in patients who had progressed after oxaliplatin-based regimen, the rate of efficieny and tolerability of addition of bevacizumab to second-line CT is exactly not known. This situation same in patients with K-ras mutant tumor. Thus the data in adding bevacizumab to mFOLFIRI will become important. From the point of this reason, we aim to evalutate datas of mFOLFIRI-B as a second line therapy of 172 patients who had progressed after oxaliplatin-based CT.

Combination of 5-FU/leucovorin is the first important regimen that had been used in mCRC patients and by this regimen 5 years OS is below the 1%[33]. Nowadays by applying modern CT regimens and metastasectomies, rate of 5 years OS is nearly equal to 30%[34].

Table 1. *General characteristics of the patients*

Characteristic		n (%)
Gender		
Female		71 (41.3)
Male		101 (58.7)
Primary tumor localization		
Colon		98 (56.9)
	Right	26 (15.1)
	Middle	28 (16.2)
	Left	44 (25.6)
Rectum		74 (43.1)
	Upper	22 (12.8)
	Middle	23 (13.4)
	Lower	29 (16.9)
Histopathology		
Adenocarcinoma		148 (86.1)
Other		24 (13.9)
Metastatic organ		
Liver		114 (66.2)
Findings indicating intraabdominal tumor invasion		54 (31.3)
Lung		43 (25.0)
Bone		19 (11.0)
Supraclavicular lymph node involvement		5 (2.9)
Spleen		3 (1.7)
Ovary		2 (1.1)
Metastasis in two organs		41 (23.8)
Metastasis in more than two organs		27 (15.6)
Serum CEA		
5 ng/mL and higher		145 (84.4)
Lower than 5 ng/mL		27 (15.6)

CEA, Carcinoembryonic antigen.

Table 2. *Other characteristics of the patients*

	n (%)
History of primary tumor operation	63 (36.6)
History of adjuvant CT	34 (19.7)
History of neoadjuvant CRT	25 (14.5)
History of adjuvant CRT	6 (3.4)
In first-line CT regimes	
Modified FOLFOX6	19 (11.1)
FOLFOX6	5 (2.9)
FOLFOX7	117 (68.0)
XELOX4	9 (5.2)
XELOX7	22 (12.8)
In second-line CT regime	172 (100.0)
Modified FOLFIRI-Bevasizumab	172 (100.0)
Third-line CT received patients	75 (43.6)
Fourth-line CT received patients	34 (19.7)
Fifth-line CT received patients	15 (8.7)

CT, Chemotherapy; CRT, Chemoradiotherapy.

Table 3. *Efficacy provided by the treatment administered*

	Month (95% CI)	%	n (%)
Median PFS	9.0 (7.6–10.3)		
Median OS	19.0 (15.1–26.2)		
1 year OS		69.0	
3 years OS		25.0	
5 years OS		13.5	
Complete response			11 (6.4)
Partial response			57 (33.1)
All response rates			68 (39.5)
Stable disease			42 (24.4)
Progressive disease			62 (36.0)
Patients who had undergone primary tumor resection			12 (6.9)
R0 resection			10 (5.8)
R1 resection			2 (1.1)
Patients who had undergone metastasectomy			14 (8.1)
R0 resection			11 (6.4)
R1 resection			3 (1.7)
Liver metastasectomy			10 (5.8)
Peritonectomy			5 (2.9)
Lung metastasectomy			5 (2.9)
Splenectomy			1 (0.5)
Patients whose serum CEA levels decreased			38 (22.0)
Patients whose serum CEA level decreased below 5 ng/mL			12 (6.9)

PFS, Progression-free survival; DFS, Disease-free survival; OS, Overall survival; CEA, Carcinoembrionic antigen.

Table 4. *Side effects caused by treatment*

Characteristic	Grade ½ side effects n (%)	Grade ¾ side effects n (%)	n (%)
All	113 (65.6)	58 (33.7)	
All hematological side effects	98 (56.9)	55 (31.9)	
Neutropenia	65 (37.7)	48 (27.9)	
Anemia	52 (30.2)	23 (13.3)	
Thrombocytopenia	41 (23.8)	19 (11.0)	
Nausea/vomiting	44 (25.6)	32 (18.6)	
Diarrhea	29 (16.9)	18 (10.4)	
Oral mucositis	32 (18.6)	14 (8.1)	
Hand foot syndrome	17 (9.8)	8 (4.6)	
Allergic reaction	8 (4.6)	2 (1.1)	
Neurotoxicity	4 (2.3)	2 (1.1)	
Hypertension			11 (6.4)
Proteinuria			7 (4.0)
Skin eruption			7 (3.9)
Gastrointestinal bleeding			4 (2.3)
Neutropenic fever			3 (1.7)
Deep vein thrombosis			2 (1.1)

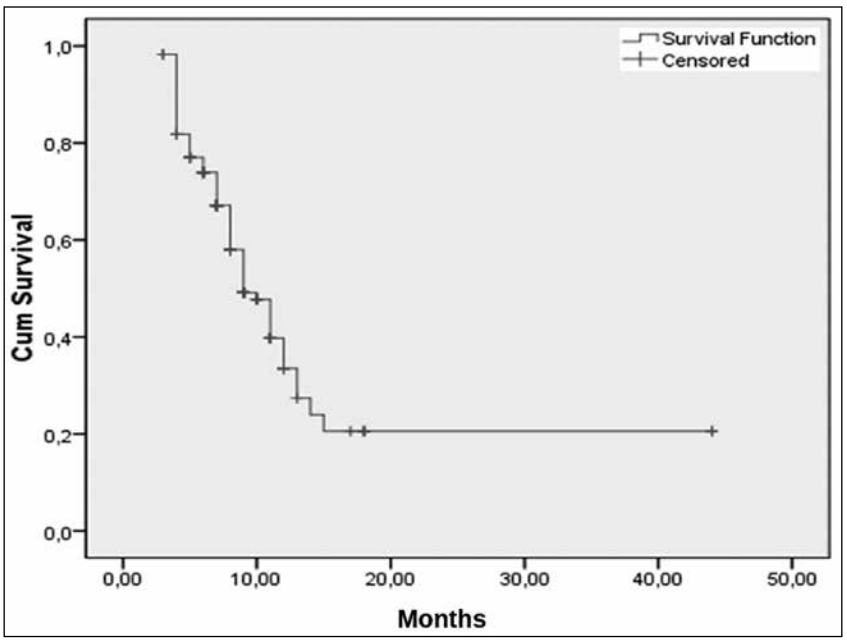

Figure 1. *Progression-free survival (median 9.0 months).*

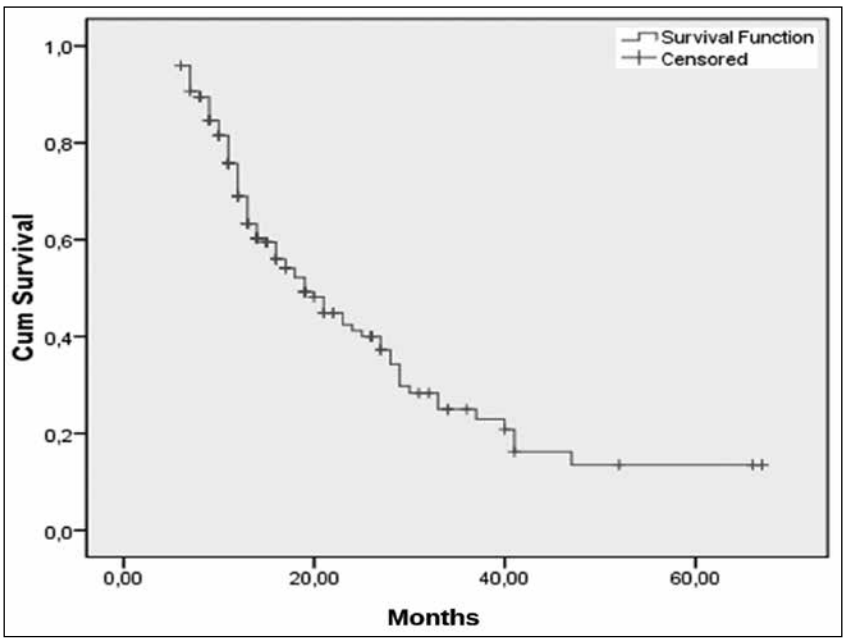

Figure 2. *Overall survival (median 19.0 months).*

Among the new chemotherapeutic agents, bevacizumab, a monoclonal antibody, is the first the drug that has been added to CT. By usage of bevacizumab in first-line therapy, survival has been getting quite longer. In a study that had used the combination of bevacizumab and irinotecan, bolus 5-FU-leucovorin (IFL regimen) in first-line therapy, by addition of bevacizumab to CT regimen, an important survival advantage has been achieved[13]. Infusional 5-FU is more effective in mCRC. By the way it has been shown that FOLFIRI regimen is much more useful comparing to IFL regimen and another study showed that the addition of bevacizumab to FOLFIRI regimen had better PFS and OS results[28,35].

There are some studies that had used a bevacizumab containing regimen as second or third line therapy in mCRC patients that progressed after first-line therapy. Regarding this, there is an important study that used oxaliplatin, 5-FU, leucoverin and bevacizumab (FOLFOX4-B) as a second-line therapy after progression of patients with mCRC. By this treatment option there was a advantage of OS[36]. As a result of showing effiency of bevacizumab in combination with oxaliplatin in second line therapy, a multicenter study using bevacizumab in combination with FOLFIRI regimen in second line treatment was performed. By this study, advantage of 8.3 months median PFS and 21.6 months median OS were achieved[37].

Although bevacizumab has survival advantage in combination with first-line CT, it has been shown that after progression of disease there is still survival advantage of using bevacizumab in combination with second-line treatment[38].

There is concensus about usage of bevacizumab in first-line therapy. It has not still being clearly defined that there is survival advantage of adding bevacizumab to mFOLFIRI regimen as a second-line therapy in patients who had previously used different CT regimens. Since mCRC patients are now huge populations, collecting data about mFOLFIRI-B as second-line therapy is becoming very important.

However, in our study, grade 3/4 toxicity was observed in 33.7% of the patients. Grade 3/4 neutropenia was observed 27.9% of the patients. Side effects of bevacizumab, hypertension and proteinuria was found to be 6.4% and 4.0%, respectively. This findings suggest that mFOLFIRI-B may be tolerated regimen for side effects.

Since this study was a retrospective study, it has disadvantages related to retrospective studies. However, regarding a subject like treatment of mCRC which concerns a large number of patients, we thought that it would be beneficial to present mFOLFIRI-B regime in the second-line treatment which showed progression under the oxaliplatin-based regime in the first-line treatment of mCRC patients to the literature, though we used retrospective data.

Consequently, we can state that mFOLFIRI-B regime provides a significant survival advantage in second-line treatment of mCRC patients in whom progression was detected after the oxaliplatin-based regime in the first-line treatment. It provides reduction in the volume and number of the metastatic tumor, makes it easy to metastasectomy, increases PFS and OS and has easly managable side effects. We think that there is a need to make prospective studies for clerance of this topic.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Use of Complementary and Alternative Medicine Methods Among Elderly People Living in Nursing Homes

Huzurevinde Kalan Yaşlılarda Tamamlayıcı ve Alternatif Tıp Yöntemlerini Kullanma Durumu

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ABSTRACT

Aim: *Complementary and alternative medicine (CAM) usage has increased among the elderly. To promote comprehensive quality care, health professionals should assess for CAM usage. This study was planned to determine the CAM usage among elderly living in nursing homes in Istanbul.*

Material and Method: *This study was made in two nursing homes in Istanbul between December 2012 and May 2013. The study sample consisted of 230 elderly.*

Results: *A percentage of 59.1 of elderly (n=136) used CAM. Herbs (55.2%) and non-herbal supplements (53.5%) were the most frequently used therapies. CAM usage rate was higher among elderly who graduated from secondary school, had chronic disorder, and used medicine regularly (p <0.05); 65.4% of them did not inform healthcare personnel.*

Conclusion: *CAM is used commonly by elderly living in nursing homes. Herbal (parsley, garlic and mint) and non-herbal supplements (honey, vitamin B, Vitamin C) were used commonly. Elderly who graduated from secondary school, had chronic disorders, and used medicines regularly preferred using CAM. Elderly generally do not inform healthcare personnel that they have used these methods.*

Key words: *complementary and alternative medicine; elderly; nursing homes*

ÖZET

Amaç: *Tamamlayıcı ve alternatif tıp (TAT) yöntemlerinin kullanımı yaşlılar arasında artmıştır. Bakım kalitesini yükseltmek için sağlık profesyonelleri TAT yöntemlerinin kullanımını değerlendirmelidir. Bu çalışma İstanbul'da iki huzurevinde kalan yaşlılarda TAT yöntemlerini kullanma durumunu saptamak amacıyla yapıldı.*

Materyal ve Metot: *Bu çalışma Aralık 2012 ve Mayıs 2013 tarihleri arasında İstanbul'da iki huzurevinde yapıldı. Çalışmanın örneklemini 230 yaşlı birey oluşturdu.*

Bulgular: *Yaşlıların %59,1'i TAT yöntemlerinden birini kullanıyordu. Bitkiler (%55,2) ve bitkisel olmayan destekler (%53,5) en çok kullanılan TAT yöntemleriydi. Ortaokul mezunu, kronik bir hastalığı olan ve düzenli tıbbi tedavi alan yaşlılar arasında TAT kullanım oranı yüksekti (p <0,05). Yaşlıların %65,4'ü TAT kullandığını sağlık personeline bilgi vermemişti.*

Sonuç: *Huzurevinde kalan yaşlılarda TAT kullanımı yaygındı. Bitkisel (maydanoz, sarımsak ve nane) ve bitkisel olmayan destekler (bal, B ve C vitamini) en yaygın kullanılan yöntemlerdir. Ortaokul mezunu, kronik bir hastalığı olan ve düzenli tıbbi tedavi alan yaşlılar TAT kullanımını tercih etmektedir. Yaşlılar genellikle bu yöntemleri kullandıklarını sağlık personeline söylememektedir.*

Anahtar kelimeler: *tamamlayıcı ve alternatif tıp; yaşlı birey; huzurevi*

Introduction

Complementary and alternative medicine (CAM) is defined by the National Center for Complementary and Alternative Medicine as a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine[1]. Although CAM have been used since the time humanity has come into existence, it has started to be used widely after the 90's. In the United States of America, use of CAM increased from 33.8% to 42.1% between 1990 and 1997[2]. CAM has increased due to factors such as symptoms of a disease, dissatisfaction with health care teams and medical outcomes, high health care charges, side effects of drugs or treatments, lack of control in their own health care practices[3–8]. In a systematic review, prevalence rates of CAM among general population has been

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reported between 5% and 74.8%[9]. CAM usage rates may differ between countries or even regions. The usage of CAM varies among cultures according to beliefs, religions, lifestyle, and probably, specific herbs that grow in certain geographical area. CAM usage in Turkey had been subject of some studies. In these studies, the percentage of CAM usage varies between 35.3% and 86.3%[10–15]. In studies carried out on elderly individuals, the percentage of CAM usage varies between 27.7% and 88%[8,16–26]. These methods have been preferred mostly by elderly who are well-educated[3,16,19] have a high socio-economical status[19,20], are female[17,19,27,28], and are younger elderly[16]. The elderly people have more chronic diseases and disabilities, uses more medications, and often needs more health care services than younger[29]. Rates of chronic diseases are positively associated with CAM usage rates[5,16,21]. As a result, more CAM use can be seen in elderly people in the future. Healthcare professionals'knowledge of the factors which ease or blocks the use of CAM is important in order to protect the health of the elderly population and maintain their safety. In the literature, it has been stated that patients/elderly who used CAM do not inform healthcare personnel, also healthcare personnel do not question CAM usage[12,15,18,30]. Health professionals should assess for CAM use and increase their understanding about the kind and reason of the CAM therapies for comprehensive and qualified care. In addition, it should be assessed whether elderly continue their own medications while using these methods and whether they benefit or get harm from these methods[18]. Although several studies on the determination of CAM methods among the elderly exist[16–18,20,21,23,24,26,31] there is only a single study carried out in Turkey[25]. Additionally there is not any study on usage of CAM among elderly living in nursing homes. Elderly living in their own houses can be followed by caregivers about medicine and CAM usage. But evaluation of the CAM usage among elderly in nursing homes should be carried out by the nurses regularly. This study was planned to determine the CAM applications and factors associated with its use among elderly people living in nursing homes in Istanbul in Turkey.

Material and Method

Sample

This study was made in two nursing homes in Istanbul in Turkey between December 2012 and May 2013. The study was conducted with 230 of the 357 (64.4%) elderly who living two nursing homes. The patients were aged 65 years and older, had no psychiatric disorder and communication problems and were conscious and consented to participate in the study. Prior to the study, Marmara University Ethics Committee permission was obtained. All elderly were made aware of the proposed study procedures and freely gave written informed consent.

Data Collection Form

Data was collected by the researchers in a comfortable setting via questionnaire method using the data collection form developed by the researchers. Data collection form included questions on socio-demographic characteristics (age, sex, marital status, educational status, economical status, chronic diseases, regular medication usage, etc.) and CAM usage (CAM types used by elderly, reasons to choose these methods, the benefits and harms of these methods, sources of information for these methods, whether the elderly report using these methods to health professionals). A total of 23 questions were asked and data collection takes approximately 15 minutes.

Data were assessed by using the SPSS 15.0 program (SPSS Inc., Chicago, IL, USA)[32]. In order to analyze the data, means, frequencies, and percentages were calculated. The t-test for independent samples was used to analyze the difference in term of age between patients who use CAM and those who do not. The difference regarding dichotomous and categorical variables between patients who use CAM and those who do not was evaluated with Pearson's chi-square test. The Fisher's exact test was used when the expected value in any box of the chi-square tables containing the dichotomous variables were below 5, and the Pearson's chi-square test was used when all or 80% of the expected values in any box of the chi-square tables containing the categorical variables were above 5. A level of significance of $p < 0.05$ was established prior to data collection.

Results

Mean age of the elderly was 71.86±6.70 years. Among 230 elderly, 61.7% were female and 62.6% were married. The majority of the elderly graduated from elementary school (44.3%), more than half of them had social security (87.4%), approximately half of them were retired (44.8%) and 67.8% had a medium level of income. In this study, 74.8% had at least one chronic disease, 73.9% were using medications regularly, 59.1% were using CAM methods (Table 1).

A percentage of 55.2 of elderly used average 5.13±3.62 (min, max: 1, 15) type herbs/herbal supplements. The

most frequently used herbs were parsley (32.6%), garlic (30.9%), mint (27.8%), black grape seed (20.9%), black mulberry (20.4%), green tea (20.4%), sage (20.4%), nettle (18.3%), and linseed (16.5%). A percentage of 53.5 of elderly used average 3.15±2.57 (min, max: 1, 11) type non-herbal supplements. The most frequently used non-herbal supplements were honey (31.7%), vitamin B (23.9%), Vitamin C (20.4%), fish oil (19.1%). Among other CAM methods, the elderly mostly used prayer (33.9%), music (18.3%), massage (9.6%), thermal spring (7%), and cupping (6.1%) (Table 2).

A percentage of 69.9 of elderly benefited and a percentage of 0.7 of elderly harmed from the CAM methods they used. Elderly frequently did not tell the healthcare personnel that they have used these methods (65.4%). The reasons for not telling the healthcare personnel were not feeling the need to tell the healthcare personnel (31.6%), or not being questioned by the healthcare personnel on this subject (30.9%) and disapproving of these methods (8.1%). When the reasons for using these methods were

Table 1. *Demographic Characteristics of Elderly*

Variables		n	%
Age (years) (mean±SD)		71.86±6.70 (min, max: 65, 91)	
Gender			
	Female	142	61.7
	Male	88	38.3
Marital status			
	Single	86	37.4
	Married	144	62.6
Education			
	Illiterate	23	10.0
	Literate	36	15.7
	Elementary school	102	44.3
	Secondary school	28	12.2
	High school	41	17.8
Social security			
	Yes	201	87.4
	No	29	12.6
Job			
	Housewife	97	42.2
	Worker	11	4.8
	Officer	3	1.3
	Retired	103	44.8
	Own business	16	7.0
Level of income			
	Poor	19	8.3
	Moderate	156	67.8
	Good	55	23.9
Presence of a chronic disease			
	Yes	172	74.8
	No	58	25.2
Regular drug use			
	Yes	170	73.9
	No	60	26.1
CAM usage			
	Yes	136	59.1
	No	94	40.9

CAM, complementary and alternative medicine; SD, standart deviation

Table 2. *The types of CAM used by elderly*

		n	%
Herbs*		127	55.2
	Parsley	75	32.6
	Garlic	71	30.9
	Mint	64	27.8
	Thyme	58	25.2
	Black grape/seed	48	20.9
	Black mulberry	47	20.4
	Green tea	47	20.4
	Sage	47	20.4
	Nettle	42	18.3
	Linseed	38	16.5
	Black cumin	28	12.2
	Radish	34	14.8
	Ginger	24	10.4
	Cinnamon	18	7.8
	Echinacea	16	7
	Chicory	14	6.1
	Gingko biloba	2	0.9
	Ginseng	2	0.9
Non-herbal supplements*		123	53.5
	Honey	73	31.7
	Vitamin B	55	23.9
	Vitamin C	47	20.4
	Fish oil	44	19.1
	Vitamin D	35	15.2
	Vitamin E	28	12.2
	Royal jelly	27	11.7
	Vitamin A	27	11.7
	Magnesium	18	7.8
	Omega 3–6–9	17	7.4
	Coenzyme Q10	16	7
Other Therapies*			
	Prayer	78	33.9
	Music	42	18.3
	Massage	22	9.6
	Thermal spring	16	7
	Cupping	14	6.1
	Acupuncture	5	2.2
	Reflexology	4	1.7
	Breathing therapy	4	1.7
	Reiki	3	1.3
	Yoga	3	1.3

CAM, complementary and alternative medicine. *More than one option was selected.

asked; the participants stated more than one reason. Elderly used these methods because these methods made them feel better (80.1%), they thought these methods were beneficial (60.3%), these methods increased immunity (32.4%), they thought these methods support medical treatments (22.8%), had less side effects (18.4%), they did not benefit from medical treatment (17.6%), these methods were cheaper (8.8%) and they did not have another option (5.9%). A percentage of 64.7 of the elderly have heard of these methods from friends and family, the media (32.4%), healthcare personnel (25%), pharmacies (8.1%), and the internet (6.6%) (Table 3).

There were a statistically significant differences between elderly who use and who do not use CAM methods regarding education level (p = 0.016), presence of a chronic disease (p = 0.011) and regular drug use (p = 0.004). CAM usage rate was higher among elderly who graduated from secondary school, had chronic disorders, and used medicines regularly. On the other hand, there were no statistically significant differences between elderly who use and who do not use CAM methods regarding age, gender, marital status, social security, job, level of income (p >0.05) (Table 4).

Table 3. *Characteristics related to CAM usage (n=136)*

	n	%
State of benefiting from CAM usage		
Yes	95	69.9
Partially	28	20.5
No	13	9.6
State of harming from CAM usage		
Yes	1	0.7
No	134	98.5
Partially	1	0.7
Healthcare personnel's state of being aware of CAM usage		
Yes	47	34.6
No	89	65.4
The reasons of healthcare personnel's unawareness*		
I did not feel the need to tell	43	31.6
The healthcare personnel does not ask questions	42	30.9
The healthcare personnel will disapprove	11	8.1
The healthcare personnel is not knowledgeable about CAM	8	5.9
The time of healthcare personnel is limited	5	3.7
Reasons for CAM usage*		
It makes me feel better	109	80.1
I think it is beneficial	82	60.3
It increases my body defense/immunity	44	32.4
Support to my medical treatment	31	22.8
It has less side effects	25	18.4
I do not benefit from my medical treatment	24	17.6
It is cheaper than medical treatment	12	8.8
I do not have any other option	8	5.9
Sources of information on CAM*		
Friends-family	88	64.7
Media-TV	44	32.4
Healthcare personnel	34	25
Pharmacy	11	8.1
Internet	9	6.6
Books/magazines	8	5.9

CAM, complementary and alternative medicine. *More than one option was selected.

Discussion

Comorbid conditions which increase with age, the elderly's wish to increase the quality of life and manage chronic problems leads them to be in search of CAM[8]. CAM methods used by elderly might vary according to geographical areas and culture. Health care providers must be aware that elderly are using CAM and are satisfied with their use[8,33]. Elderly may benefit from some CAM methods but during some CAM methods usage, undesired and even life-threatening side effects may occur. Health professionals play an important role in defining these side effects in early phases, and take precautions. Therefore, health professionals should question elderly on CAM usage[34].

The Frequency of CAM Usage

In this study, more than half of the elderly (59.1%) used at least one of the CAM methods. In studies carried out on elderly about CAM usage, CAM usage rates vary between 27.7% and 88%[8,16–26]. Because different CAM methods have been investigated in studies, different results on the frequency of CAM usage might have been obtained. Findings of this study are parallel to the literature.

CAM Methods Used by Elderly

The most preferred CAM type in this study was herbs. A percentage of 55.2 of elderly used average 5.13±3.62 (min, max: 1, 15) type herbs/herbal supplements. In parallel to this findings, Astin et al.[16] and Loera et al.[23] found that herbs are the most common CAM type used by the elderly. Among CAM methods, the use of herbs has increased in the last two decades.[35] In general; elderly people believe that herbs are safe, side effect free, and non-addictive. Because herbs are assumed to be natural and safe, they are sold in many markets and stores, are easily accessed and do not need to be prescribed[36].

Table 4. *Factors associated with CAM usage (n=230)*

		Non CAM users (n=94)	CAM users (n=136)	p
Age (years) mean±SD		71.61±6.37	72.03±6.94	0.633[h]
Gender				
	Female	56 (58.0)	86 (84.0)	0.524[t]
	Male	38 (36.0)	50 (52.0)	
Marital status				
	Single	30 (35.6)	57 (51.4)	0.124[t]
	Married	64 (58.4)	79 (84.6)	
Education				
	Illiterate	8 (9.4)	15 (13.6)	***0.016**[t]
	Literate	14 (14.7)	22 (21.3)	
	Elementary school	51 (41.7)	51 (60.3)	
	Secondary school	4 (11.4)	24 (16.6)	
	High school	17 (16.8)	24 (24.2)	
Social security				
	Yes	84 (82.1)	117 (118.9)	0.546[ŧ]
	No	10 (11.9)	19 (17.1)	
Job				
	Housewife	36 (39.6)	61 (57.4)	0.536[ŧ]
	Worker	3 (4.5)	8 (6.5)	
	Officer	2 (1.2)	1 (1.8)	
	Retired	45 (42.1)	58 (60.9)	
	Own business	8 (6.5)	8 (9.5)	
Level of income				
	Poor	7 (7.8)	12 (11.2)	0.808[t]
	Moderate	66 (63.8)	90 (92.2)	
	Good	21 (22.5)	34 (32.5)	
Presence of a chronic disease				
	Yes	69 (76.4)	118 (110.6)	***0.011**[t]
	No	25 (17.6)	18 (25.4)	
Regular drug use				
	Yes	60 (69.5)	110 (100.5)	****0.004**[t]
	No	34 (24.5)	26 (35.5)	

*p <0.05; **p <0.01; [h]t-test; Ŧ Pearson's chi-square test; [ŧ]Fisher's exact test.
The values in the parentheses show the expected values.
CAM, complementary and alternative medicine; SD, standart deviation.

In this study, the most preferred herbs by the elderly are parsley, garlic, mint, thyme, black grape seed, black mulberry, green tea, sage, nettle, and linseed; respectively. It has been reported that chamomile, heliotrope and other herbal teas including licorice, hibiscus, vervain, linden[17], garlic[16,20], echinacea[18], gingkgo[16,20], ginseng[16,20] and phytotherapeutic products[27] are commonly consumed by the elderly. Consistent with the literature, in this study, herbs have been preferred primarily; however, the herb kinds that the elderly use in our study are different. The reason for this may be related to the variety of herbs that exist in a specific region and certain geographical and climate conditions.

In this study, herbs and non-herbal supplements were used frequently by elderly (including multivitamins). A percentage of 53.5 of elderly used at least one type non-herbal supplements. Mean non-herbal supplement number/type used by elderly were 3.15±2.57. The use of dietary supplements such as vitamins and multivitamins are increasing around the world. In the USA, approximately half of the adult population regularly consumes one or more dietary supplements[37]. In this study, we have observed that the elderly have used non-herbal supplements such as honey, vitamins (vitamin B, vitamin C, vitamin D, vitamin E, and vitamin A; respectively), fish oil, royal jelly, magnesium, omega 3-6-9, and coenzyme Q10 at rates differing between 7% and 31.7%. Previous studies showed that elderly individuals mostly use vitamin E[18,20], Ca[20,26], magnesium[26], iron[26], vitamin C[18,20], vitamin D_3[26], B_{12}[26], folic acid[26], chondroitin sulphate[18] and minerals[18]. Our study results are in line with the literature.

When we examined other CAM types, we found that the elderly mainly used prayer (33.9%), which was followed by music (18.3%), massage (9.6%), and thermal springs (7%); respectively. When we examined the literature, other mainly used CAM types included prayer[31], spiritual practices[19], massage[8,20,31], exercise/movement therapies[19], special diets[19], chiropractice[8,19,24], meditation[19,20,24,31] and breathing exercises[20]. The reason that praying was the most preferred method in this study is thought to originate from the fact that elderly people resort to religious practices in terms of solving health problems in Turkey, where the majority of the population is Muslim. In this study, we have observed that applications such as breathing exercises, meditation, chiropractice, acupuncture, hypnosis, yoga and energy therapies are rarely or never used. The reason for this may be CAM practitioners not being common in Turkey and Turkish elderly not being informed about these methods.

Informing Health Professionals about CAM Usage

In this study, although most of the (69.9%) of the elderly who used CAM methods have told that they benefited from these methods, it was found that 65.4% of them did not inform healthcare personnel.

The elderly reported that the reasons for not telling included not feeling the need to tell (31.6%), or not being questioned by the healthcare personnel about CAM usage (30.9%) and not approving such usage (8.1%). Also, in previous studies, it was found that the elderly substantially benefited from CAM methods and that they did not tell the healthcare personnel about these methods at varying rates of 47% and 58% [8,16]. The reasons for this include 'not being asked by healthcare personnel on the subject, the participants not knowing that they should have told they used these methods and thinking that it is not important for their care'[8]. Our research findings are in parallel with these results. In summary, the elderly being afraid to share information with the healthcare personnel about the usage of CAM methods causes a weak

communication between the elderly and the healthcare personnel. Unless the obstacles related to information sharing are noticed and an open communication is provided, the elderly and the healthcare personnel will be less aware of the interaction between traditional medical treatments and CAM methods[16].

The Reasons for CAM Usage

It was found that the elderly use these methods because they felt good (80.1%), CAM are beneficial (60.3%), CAM increased body defense/immunity (32.4%), they did not benefit from medical treatment (17%), CAM supported to medical treatment (22.8%), and CAM's side effects were fewer compared to traditional medical treatments (18.4%). In the literature, the elderly people reported that they used CAM methods due to reasons similar to those found in our study, such as being dissatisfied with traditional medical treatment[16], fearing medication side effects[16], improving the general state of health[8,16], treating health problems[8] and staying healthy[31].

Sources of Information

When we examined how the elderly reached sources of information on these methods, it was determined that 64.7% of the participants have heard of these methods from friends and family, the media (32.4%), healthcare personnel (25%), pharmacies (8.1%), and the internet (6.6%). Schnabel et al.[26] and King and Pettigrew[31] also stated that elderly individuals used these methods because they were advised to do so by friends-family, doctors, pharmacists, medical or nonmedical practitioners, and the TV-radio or they chose to do so on their own. Many patients emphasize that they want to get involved in the diagnosis, planning and caring processes regarding their illness. In order to do this, they receive information through various sources. During the process of decision making about health care, open communication should be established and judgmentalism should be avoided in order to ease the patient's acquisition of correct and reliable information. In every stage of treatment, healthcare personnel should evaluate the options with patients before providing traditional medical treatment so that they can prevent insensible and secret use of CAM methods[38].

Factors Associated with CAM Usage

In this study there were statistically significant differences between elderly who use and who do not use CAM methods in terms of education level; secondary school graduates were using CAM more. Similar to this study's results, it has been reported that CAM usage is more common among people with higher levels of education[16,19,21].

In this study, the majority of the elderly individuals had one chronic disease (74.8%) and CAM usage was more common among elderly individuals who had a chronic disease and who used medications regularly. Elderly individuals use an increasing amount of medication due to chronic health problems that increase during old age. Thus, this condition increases both the morbidity and mortality risks related to medication side effects[39]. Elderly individuals tend towards CAM methods due to both physiological factors such as chronic diseases and unwanted situations caused by multiple medications use[16,20,8]. Results of relevant studies support our findings. In previous studies, it has been reported that CAM usage is more common among people who have multiple health problems[21,23] those who suffer from health problems such as chronic pain[8], arthritis[8,16] and depression/anxiety[16] and those practice medication[16].

In this study, there were no statistically significant differences between elderly who use and who do not use CAM methods regarding age, gender, marital status, social security, job, level of income. Cheung et al.[8] found that there is no relationship between socio-demographic characteristics such as age, gender, marital status and income level and CAM usage. Cheung et al.'s results are parallel to this study results. But other studies that evaluate CAM usage according to sociodemographic characteristics among the elderly, it was reported that females[17,19,21,23], young elderly[16,21], unmarried[23] and high income level[19] CAM methods were more frequently used.

CAM is used commonly by elderly people living in nursing homes in Istanbul in Turkey. Herbal supplements (parsley, garlic and mint) and non-herbal supplements (honey, vitamin B, Vitamin C) were used commonly. Elderly generally do not inform healthcare personnel that they have used these methods. Most of the elderly who used CAM methods benefit from these methods without getting any harm. The rate of CAM usage is higher among elderly who graduate from secondary school, have chronic disorders, and use medicine regularly.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Analysis of Syrian Refugee Patients Treated With the Diagnose of Hydrocephalus: The Study of 28 Cases

Hidrosefali Tanısıyla Tedavi Gören Suriyeli Mülteci Hastaların Analizi: 28 Olgunun İncelenmesi

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ABSTRACT

Hydrocephalus is a condition which results from some abnormalities in normal pathology of cerebrospinal fluid in the brain (CSF) and dilatation of ventricles, occurring with sometimes increased pressure and sometimes without any pressure and it displays various clinical findings. Hydrocephalus does not contain only the pathological entity; it involves a wide pathological group as well. Therefore, though it is possible to make various classification for hydrocephalus, it can be divided into two groups as congenital and acquired in terms of etiological. The exact diagnosis of hydrocephalus is determined by screening neural tissue. These screening methods are transfontanellar ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI). The main treatment for hydrocephalus is surgical. The fundamental aim in surgical treatment is to make parenchymal thickness 3.5 cm by reducing the intracranial pressure (ICP) to normal levels in order to increase brain tissue volume. In our research, we retrospectively studied on 28 Syrian refugees treated because of hydrocephalus for one year. We assessed the patients' age, sex, complaint, etiology, factors during the disease, shunt infection, shunt dysfunction, surgical complications and post-operative findings. We searched for the age distribution of the patients, the number of men and women and the factors seen during the disease. We classified the complaints of the patients, etiological factors and the developing complications on the patients by calculating their numbers. We assessed the improvement of the patients' complaints after surgical operation and the continuing situation for 4 months follow-up on average.

Key words: *hydrocephalus; refugee; surgery*

ÖZET

Hidrosefali, BOS'un normal patofizyolojisindeki bir takım bozukluklar sonucu ortaya çıkan, ventriküllerde genişleme, bazen basınç artışı ile, bazen de basınç artışı olmadan karşımıza çıkan ve değişik klinik bulgular veren bir durumdur. Hidrosefali tek bir patolojik antite olmayıp geniş bir patoloji grubunu içerir. Bu nedenle hidrosefalide çok çeşitli sınıflamalar mümkün olmakla birlikte etyolojik olarak konjenital ve edinsel olarak ikiye ayrılabilir. Hidrosefalinin kesin tanısı nöral dokunun görüntülenmesi ile konur. Bu görüntüleme yöntemleri; transfontanel ultrasonografi (USG), bilgisayarlı beyin tomografisi (BBT) ve magnetik rezonans görüntüleme (MRG)'dir. Hidrosefalinin tedavisinde asıl tedavi cerrahidir. Cerrahi tedavideki asıl amaç kafa içi basıncını (KİB) normal değerlere indirip beyin dokusu volümünü artırarak serebral parankim kalınlığını en az 3,5 cm'ye ulaştırmaktır. Biz bu yazımızda1 yıl içinde hidrosefali nedeniyle tedavi edilen 28 Suriyeli Mülteci hastanın retrospektif olarak incelemesini yaptık. Hastaların yaş, cinsiyet, şikayet, etyoloji, hastalığa eşlik eden faktörler, şant enfeksiyonu, şant disfonksiyonu, cerrahi komplikasyon ve postoperatif takip bulgularını değerlendirdik. Hastaların yaş dağılımı, kadın-erkek sayısı ve hastalığa eşlik eden faktörleri araştırdık. Hastaların şikayetleri, etyolojik faktörler ile hastalarda gelişen komplikasyonlar, sayılarını hesaplayarak sınıflandırdık. Hastalara yapılan cerrahi sonrası hastaların şikayetlerindeki düzelme, devam etme hallerini ortalama 4 aylık takiple değerlendirdik.

Anahtar kelimeler: *hidrosefali; mülteci; cerrahi*

Introduction

Hydrocephalus is a disorder whose physiopathology is complicated and it occurs when cerebrospinal fluid (CSF) builds up too much in ventricles and subarachnoid space[1,2]. Although it often results from either the abnormality in CSF oscillation or the prevention of CSF from flowing, it could also develop from too much productivity of CSF as in choroid plexus tumours[3,4]. In adult patients, normal pressure hydrocephalus (NPH) is mostly seen, while in child patients, non-communicable hydrocephalus (NCH) is seen more often[3–5]. In this study, retrospective assessment of 28 Syrian refugee patients operated with the diagnosis hydrocephalus in our clinic was performed.

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Material and Method

Between the dates 1 January 2014 and 31 December 2015, 28 Syrian refugee patients operated with the diagnosis hydrocephalus were retrospectively studied in neurology clinic in Dr. Ersin Arslan Training and Research Hospital. We assessed the patients'age, sex, complaint, etiology, factors during the disease, shunt infection, shunt dysfunction, surgical complications and post-operative findings. The age distribution of the patients, the number of men and women and the factors seen during the disease were searched. The complaints of the patients, etiological factors and the developing complications on the patients were classified by calculating their numbers. The improvement of the patients'complaints after surgical operation and the continuing situation for 4 months follow-up were assessed.

Results

Thirteen of 28 patients operated in our clinic were men (46.4%) and the rest (15) were women (53.6%). The average age of the patients whose age frequencies ranging from 2 months to 76 years is 8 months. Of the patients, 21 (75%) were smaller than 1-year-old, whereas 3 (10.7%) were mature. The age of other 4 patients changed between 1 and 12 years old (Table 1). It was determined that 23 of the patients (82.1%) came to our clinic with the complaint of head circumference growth, 3 of them (% 10.7) with walking abnormalities and urinary incontinence and 2 of them (7%) with lack of head control, nausea and vomiting (Table 2). In the table of hydrocephalus, it was shown that the 8 of the patients have Chiari malformation (28.5%), 2 of them (7%) have corpus callosum dysgenesis/agenesis, 2 of them (7%) have arachnoid cyst, 1 of them (3.5%) has mega cisterna magna, 2 of them (7%) have porencephalic cyst and 1 of them (3.5%) has cerebellar hypoplasia. It was shown that 11 patients (39.3%) have spinal dysraphism (meningocele/meningomyelocele/lipomeningomyelocele). For 8 patients (28.5%), there was no other companion disease with hydrocephalus (Table 3). It was determined that 16 of the patients (57%) have congenital hydrocephalus, while 3 of them (10.7%) have NPH. In the diagnosis of all patients computed tomography (CT) was used. Magnetic resonance screening was practised to 14 patients followed (50%) who have intracranial pathologies such as Chiari malformation, corpus callosum dysgenesis/agenesis, arachnoid cyst, mega cisterna magna, porencephalic cyst and cerebellar hypoplasia. In the diagnosis of hydrocephalus, together with the clinic evans ratio which was calculated by being measured in CT was benefitted. It was observed that evans ratio was between% 40 and 50 for 3 of the patients (10.7%) and the ratio was higher than 50% in 25 patients (89.3%). It was detected that 3 patients whose evans ratio changes from% 40–50 were in adult age and all these 3 patients had NPH. Of our patients, 7 of them (25%) were the ones who were operated in Syria before and re-operated because of shunt dysfunction in our clinic, whereas 21 of them were diagnosed and operated in our clinic for the first time. The average post-op duration of the patients who didn't have any intraoperative complication was 5 months (2 months-1 year). Within the length of follow-up, because of the shunt dysfunction, shunt revision was done for only 2 of the patients (7%), while no other complication was observed in other patients (Table 4).

Table 1. *The distribution of the patients according to their age and sex*

Age	Man	Woman	Total
0–1 year	11	10	21
1–12 year	0	4	4
>18 year	2	1	3

Table 2. *The distribution of the complaints of patients*

Complaint	Number of patients (%)
Head circumference growth	23 (82.1)
Walking abnormalities and urinary incontinence	3 (10.7)
Lack of head control, nausea and vomiting	2 (7)

Table 3. *Accompanying diseases*

Disease	Number (%)
Spinal dysraphism	11 (39.3)
Chiari malformation	8 (28.5)
Corpus callosum dysgenesis/agenesis	2 (7)
Arachnoid cyst	2 (7)
Porencephalic cyst	2 (7)
Mega sisterna Magna	1 (3.5)
Cerebellar hypoplasia	1 (3.5)

Table 4. *Complications developing after surgery*

Complications	Number (%)
Shunt dysfunction	2 (7)
Not developing any complication	26 (93)

Discussion

Hydrocephalus is a condition which results from some abnormalities in normal pathology of cerebrospinal fluid in the brain (CSF) and dilatation of ventricles and which is encountered with sometimes increased pressure and sometimes without any pressure and which displays various clinical findings[6]. Hydrocephalus is not only a pathological entity; but it involves a wide pathological group as well. Therefore, though it is possible to make various classifications for hydrocephalus, it can be divided into two groups as congenital and acquired in terms of etiological[7]. Congenital hydrocephalus gives findings in early stage and it occurs depending on aqueduct stenosis, atresia of the foramen of Monro, Arnold-Chiari and Dandy-Walker malformations, benign intracranial cysts, infections, intraventricular haemorrhages, genetic defects and teratogens[8]. The most accompanying pathogen to congenital hydrocephalus is spinal dysraphism (meningocele/meningomyelocele) condition and hydrocephalus is seen in most of the patients with spinal dysraphism[9]. In our series, spinal dysraphism accompanied to 11 patients from 28 (39.3%). From this aspect, our study displays suitability with the literature. Apart from spinal dysraphism, in 8 of the patients (28.5%) Chiari malformation, in 2 of them (7%) corpus callosum dysgenesis/agenesis, in 2 of them (7%) arachnoid cyst, in one of them (3.5%) mega cisterna magna, in 2 of them (7%) porencephalic cyst and in one of them (3.5%) cerebellar hypoplasia accompanied to hydrocephalus table. No pathology accompanying to hydrocephalus was observed in 8 patients (28.5%). Acquired hydrocephalus are the ones resulting from tumours, intracerebral or intraventricular haemorrhages and infections.

In the diagnosis of hydrocephalus, history, complaint and physical examination are important. The presence of pathologies accompanying to hydrocephalus such as meningomyelocele, growth head according to the age, tight and fluffy fontanel and separated sutures are the warning signs for the diagnosis. However, the exact diagnosis of hydrocephalus is made with the screening of neural tissue. These screening methods are transfontanellar ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) [10]. Transfontanellar ultrasound is preferred particularly in prenatal period and premature infants. It has some advantages such as making bedside work-up, causing radiation, stipulating no sedation and being repeatable in required frequencies. The most crucial disadvantages are the lack of imaging quality and the lack of assessment of posterior fossa. CT is the most commonly used screening method since it scarcely stipulates sedation and its imaging quality is higher. The most important disadvantage of CT is the patient's exposure to radiation[11]. Therefore, CT is avoided in infants and new-borns because of long-term concerns of radiation. However, MRI shows the accompanying pathology to hydrocephalus and anatomical details with high screening quality and could image cerebrospinal fluid in the brain (CSF) dynamically[12]. Although it is superior than other screening methods from this point, it is difficult to use in early infancy period since it stipulates sedation and lasts longer. For all of our patients, CT was preferred as radiological imaging since the important part of the patients is within the infancy period and since it is faster, but MRI was done to study the pathology thoroughly on 14 patients (50%) detected intracranial pathology accompanying to hydrocephalus in CT.

Though carbonic anhydrase inhibitors and osmotic diuretics were tried to reduce CSF in the treatment of hydrocephalus, the effect of this treatment is temporary and the main treatment is surgical[13]. The fundamental aim in surgical treatment is to make parenchymal thickness 3.5 cm by reducing the intracranial pressure (ICP) to normal levels and increasing brain tissue volume. Here, the cortical thickness is regarded as one of the criteria in order to save cognitive functions of the patients[13]. The most used method in surgical treatment is the process to transfer CSF in ventricles to pleura, atrium or peritoneum with the help of a catheter[14,15]. Another surgical treatment alternative is the third ventriculostomy which is especially effective on aqueduct stenosis. However, this method is insufficient for the cases of communicating hydrocephalus[16]. In our series, medium pressure ventriculoperitoneal shunt was inserted in all cases and postoperative results were evaluated as highly favourable.

The most important complication of shunt application used in the treatment of hydrocephalus is the development of shunt dysfunction owing to mechanic or infective reasons. About half of shunt dysfunctions occurs within two years after shunt is inserted[17,18]. In this case, hydrocephalus clinic that exists on the patient before operation would re-appear. To diagnose shunt dysfunction earlier, necessary information should be given to the patient and his relatives and postoperative

condition should be closely followed. In our series, in only 2 patients (7%) shunt dysfunction developed and shunt revision operation was performed with early diagnosis. It was observed that in both patients, dysfunction developed due to obstruction development in the catheter and not observed any infective table.

The survival rate of the patients with hydrocephalus is around 90%, although it changes depending on prognosis etiology, anomalies accompanying to the disease, developing post-op complications and early or late interventions to these complications[19]. However, in untreated hydrocephalus cases, about half of the patients dies in the first 3 years and an important part of them ends up with mortality before the patient reaches maturity[17].

In recent years, with the increasing violence in the Middle East, especially in Syria, an intense refugee immigration started across the countries in the region. The most important one among these countries is the republic of Turkey owing to its neighbourhood with Syria. The refugees might expose to discrimination in the countries they reside and they can be deprived of the most basic human rights. Education, accommodation, food supply and medical services consist of the primary ones of these rights. Required aid has been given to the refugees either from the state or from the foundations and local people in our country. The chief one of this aid is the right of refugees to benefit from free medical services.

Gaziantep city houses many Syrian refugees as it borders with Syria and since it is one of the biggest cities in South-East Anatolia. In this study, we retrospectively searched for 28 Syrian refugee patients treated because of hydrocephalus only within a year in Dr. Ersin Arslan Training and Research hospital. We assessed the patients'ages, sexes, complaints, etiologies, factors during the disease, shunt infection, shunt dysfunction, surgical complications and post-operative findings. We searched for the age distribution of the patients, the number of men and women and the factors accompanying with the disease. We classified the complaints of the patients, etiological factors and the developing complications on the patients by calculating their numbers. We assessed the improvement of the patients'complaints after surgical operation and the continuing situation for 4 months follow-up. We wished to contribute to ease their sorrow and problems of the people who came down to refugee position in the region.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluating the Ability of the Modified IIEF-5 Questionnaire to Determine the Etiopathogenesis of Erectile Dysfunction

Erektil Disfonksiyonu Olan Hastada Etiyolojinin Belirlenmesinde Modifiye IIEF-5 Formunun Etkinliğinin Belirlenmesi

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ABSTRACT

Aim: *The aim of this study, to evaluate the ability of questions added International Index of Erectile Function-5 (IIEF-5) questionnaire differentiating the underlying etiopathogenesis of erectile dysfunction (ED).*

Material and Method: *The questions of the modified IIEF-5 were asked the patients, and scores below 21 were considered as ED. With added questions, smoking and drinking habits and the presence of diabetes mellitus, hypertension and coronary heart disease were recorded. The masturbation habits and night erections were also questionned. The patients were then sub-divided into 3 groups, namely psycogenic, arteriogenic and cavernosal ED. The results of questionnaire were correlated with penile Doppler ultrasonography (PDU) results.*

Results: *The mean age of the 100 patients was 45.25±12.67, and the mean duration of ED was 40.97±58.11 months. When diagnostic ability of the modified IIEF technique was compared with PDU, the 1 st, 2nd and 3rd methods accurately diagnosed 49%, 75% and 79% of the patients, respectively. The kappa correlation coefficient was 18, 57 and 73 for techniques 1, 2 and 3, respectively. IIEF scores of organic and psycogenic groups were 9.92±3.94 and 12.82±4.37 (p = 0.001). Mean IIEF scores of arterial ED, venous ED and pyscogenic ED groups were 8.6±3.34, 12.32±3.86, 12.32±3.86, respectively and the arterial ED group was significantly different (p <0.001).*

Conclusion: *Though the majority of the techniques to determine the etiopathogenesis of ED are invasive, modified IIEF is a simple and accurate technique, especially with the third step and useful for the urologists in their clinical practice.*

Key words: *modified IIEF-5; erectile dysfunction; etiopathogenesis*

ÖZET

Amaç: *Çalışmamızın amacı, eklenen sorularla modifiye edilmiş uluslararası ereksiyon işlevi değerlendirme formunu (IIEF-5) kullanarak erektil disfonksiyonlu (ED) hastalarda altta yatan etiyolojik faktörü öngörebilmektir.*

Materyal ve Metot: *Modifiye IIEF-5 formu erektil disfonksiyonu olan hastalara uygulandı ve skoru 21'in altında olan 100 hasta ED olarak kabul edilip çalışmaya dahil edildi. Eklenen sorularla hastaların sigara ve alkol alışkanlıkları, diabetes mellitus, hipertansiyon ve koroner arter hastalıkları sorgulandı. mastürbasyon alışkanlıkları ve gece ereksiyonları da ayrıca sorgulandı. Hastalar alınan cevaplara göre psikojenik, arteriyojenik ve kavernozal ED olarak 3 alt gruba ayırıldı. Formun sonuçları penil Doppler ultrason sonuçları ile karşılaştırıldı.*

Bulgular: *Çalışmaya dahil edilen 100 hastanın ortalama yaşı 45,25±12,67 ve ortalama ED süresi 40,97±58,11 ay olarak hesaplandı. Modifiye IIEF-5 formunun etiyolojiyi öngören sonuçları ile penil doppler ultrasonografi sonuçları karşılaştırıldığında 1., 2. ve 3. yöntemler için hastaların sırasıyla %49, %75 ve %79'u doğru tanı aldı. kappa korelasyonu da sırasıyla 18, 57 ve 73 olarak belirlendi. Ortalama IIEF-5 skorları organik ve psikojenik gruplar için sırasıyla 9,92±3,94 ve 12,82±4,37 olarak tespit edildi (p = 0,001). Arteriyel, venöz ve psikojenik gruplar için ortalama IIEF-5 değerleri ise sırasıyla 8,6±3,34, 12,32±3,86, 12,32±3,86, iken arteriyel grubun sonuçlarının diğer gruptan istatistiksel olarak farklı olduğu gözlendi.*

Sonuç: *ED etiyolojisinin belirlenmesinde kullanılan yöntemlerin çoğu invaziv iken, modifiye edilmiş IIEF-5 formu ED olan hastalarda etiyolojiyi belirlemede ve tedavide ürologların klinik pratikte yararlanabileceği basit ve doğru sonuçlar veren bir testtir.*

Anahtar kelimeler: *modifiye IIEF-5; erektil disfonksiyon; etiyopatogenez*

Introduction

Erectile dysfunction (ED) affects more than 52% of men aged 40–70 years[1]. It is estimated that over 152 million men worldwide are affected by ED; more than 322 million men will be affected in 2025[2,3]. Erectile dysfunction is defined as the persistent inability to achieve or maintain penile erections of sufficient value to engage in satisfactory sexual activity[4]. The most common underlying etiologic factors of ED are organic causes, particularly vascular insufficiency and psychological causes[5]. According to pathophysiology, ED is classified as organic (vasculogenic, neurogenic, hormonal, drug-induced, or anatomic/structural), psychogenic or mixed type[6]. Commonly used

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diagnostic techniques –such as penile Doppler ultrasonography (PDU), nocturnal penile monitoring, intracavernosal pharmacological tests, and cavernosometry– can yield inaccurate results, and some of these techniques are invasive. Despite its disadvantages, imaging related to ED is dominated by PDU[5]. However, patient self-reported techniques, such as the simplified version of the International Index of Erectile Function (IIEF), which consists of only 5 items (IIEF-5), has been proposed as a sexual assessment method to diagnose and classify ED in clinical trials[7,8].

Here, we evaluate how well questions added to the IIEF-5 questionnaire can differentiate the underlying etiopathogenesis of ED. We correlated the results of the modified IIEF-5 questionnaire with the PDU results.

Material and Method

We included 132 patients with established ED in our study; we required that all of the patients in our cohort be followed up for a minimum of three months. The majority of patients were diagnosed between 2001 and 2011. All patients complained of the inability to achieve and/or maintain an erection of sufficient rigidity and duration to permit satisfactory sexual performance. We obtained a detailed medical and sexual history from each patient. We then conducted a physical examination of each patient, including an assessment of genitourinary, endocrine, vascular, and neurologic systems. We also obtained laboratory tests, including fasting glucose, a lipid profile, a morning sample of total testosterone, and PSA level, in men over the age of 45.

Exclusion criteria for this study included the presence of any neurological or hormonal (including testosterone, prolactin and thyroid hormones) disorders, a low intellect level, abnormal penile examination (Peyronie disease), a past medical history of any pelvic surgery or drug use that may cause ED and liver or kidney dysfunction. Thirty-two patients were excluded from the study based on these criteria.

The patients were informed about the aim of the study, and written informed consent was obtained from all patients. Next, we asked questions from the modified IIEF using a face-to-face technique. IIEF-5 scores below 21 were considered to be representative of ED. The questions that we added were related to smoking and drinking habits and the presence of diabetes mellitus (DM), hypertension (HT) and coronary heart disease (CHD). The patients'masturbation habits and night erections were also questioned.

We then divided the patients into three groups based on their responses to the modified IIEF-5 questions. We conducted this division using three different techniques. In the first technique, patients with a smoking history of at least 10 pack-years or patients with a history of alcohol abuse or a past medical history of DM, HT or CHD for at least 5 years were considered to represent cases of 'organic'ED; all other patients were sub-grouped as 'psychogenic' ED. The patients with organic ED were sub-classified into 2 groups as follows: patients with a chief complaint of inability to achieve a rigid erection (question 3 on the IIEF) were considered to be cases of 'arteriogenic' ED, and patients with a chief complaint of the inability to preserve an erection (question 4 on the IIEF) were considered to be cases of 'cavernosal' ED.

In the second technique, patients who maintained successful masturbation habits and night erections were considered to be 'psychogenic'. The patients in the organic group were sub-classified into 2 groups as follows: patients with a chief complaint of the inability to achieve a rigid erection (question 3 on the IIEF) were considered to be cases of 'arteriogenic' ED, and patients with a chief complaint of the inability to preserve an erection (question 4 on the IIEF) were considered to be cases of 'cavernosal' ED.

In the third technique, we modified our methodology outlined in the previous paragraph. Patients with psychogenic ED were placed in the cavernosal ED group if their chief complaint was the inability to preserve an erection. As a summary, patients were sub-divided into three groups: namely psychogenic, arteriogenic and cavernosal ED.

Patients then underwent color-Doppler ultrasonography using a Hitachi EUB 555 high-resolution imager with a 7.5 MHz linear probe. We monitored arterial and venous blood flow before and 15 minutes after a 60 mg intracavernosal papaverine injection. The following combination of maximum systolic flow (MSF) above 35 cm/second, end-diastolic flow (EDF) less than 5 cm/second and resistive index (RI=MSH-DSH/MSH) above 0.9 cm/second was considered to be a 'normal'PDU result. Patients with a MSH below 35 cm/second were considered to exhibit 'arterial insufficiency' regardless of their DSH; the remaining patients with a DSH above 5 cm/second were considered to have 'cavernosal insufficiency'.

We then compared the groups determined using the modified IIEF technique and PDU; we employed a

kappa test to make these comparisons. We set significance at 5%. Taking the PDU results as a definitive diagnosis, we compared the accuracy of the modified IIEF with the PDU results. Kappa values between 21 and 40 were considered to be 'correlated', and values between 41 and 60 were considered to be 'moderately correlated.' Values between 81 and 100 were considered to be 'highly correlated'. Furthermore, we determined sensitivity and specificity of the modified IIEF for diagnosing the three sub-groups of ED patients.

We measured the percentage distribution of risk factors according to Doppler USG. We analyzed the IIEF results of patients with psychogenic and organic ED using the Kruskal-Wallis and Mann-Whitney tests.

Results

The mean age of the 100 patients included in our study was 45.25±12.67 years (range: 22–75 years), and the mean duration of ED was 40.97±58.11 months (range: 3–384 months). Sixty-one patients described night erections, and 19 patients described successful masturbation. A history of DM, HT and smoking was recorded in 26, 5 and 59 patients, respectively. All of these patients except for one were older than 40. Sixty-one patients were older than 40, and 39 patients were younger than 40. The mean age of patients older than 40 was 53.34±8.55 years, and the mean age of patients younger than 40 was 32.59±5.75 years.

The mean duration of smoking was 254.94±144.04 months, and all patients except for one had been smoking for at least 5 years.

When we compared the diagnostic ability of the modified IIEF technique with PDU, the 1st, 2nd and 3rd techniques accurately diagnosed 49%, 75% and 79% of the patients, respectively. The kappa correlation coefficient was 18, 57 and 73 for techniques 1, 2 and 3 of the modified IIEF, respectively. The patient distribution with the modified IIEF technique is shown in Tables 1–3.

The mean IIEF scores of the organic and psychogenic groups were 9.92±3.94 and 12.82±4.37, respectively ($p = 0.001$). The mean IIEF scores of the arterial, cavernosal and pyschogenic ED groups were 8.6±3.34 (range: 4–15), 12.32±3.86 (range: 5–19) and 12.32±3.86 (range: 5–19), respectively, and the arterial ED group was significantly different ($p < 0.001$). With the third division technique, which yielded the most reliable results, results that were consistent with those of PDU were obtained for 79 of the patients (79%).

Discussion

Erectile dysfunction is a problem more frequently observed in the elderly population; symptoms typically become more serious with increasing age[9]. Vasculogenic and psychogenic factors are among the more common underlying etiological factors of ED[10]. Smoking, DM, CHD, HT and metabolic syndrome are among the most prevalent risk factors that increase significantly the incidence of ED[10,11]. However, the presence of more than one of these factors in the same patient and the concomitant use of drugs that may cause ED poses a challenge for identifying novel risk factors. Similarly, the chronic diseases noted above have the potential to cause psychological problems and may cause psychogenic ED.

Although the risk factors highlighted above are known to predispose a patient to ED, not all patients with these factors develop ED. It is also difficult to determine whether there is an organic component of ED in patients with these risk factors. It is less-well known whether the duration of these risk factors or the severity of these diseases are correlated with ED.

Table 1. *Comparison of PDU results and etiological factors as determined by technique 1*

	Doppler			
Comparison of Step 1 and PDU	Arterial ED	Psycogenic ED	Venous ED	Total
Arterial ED (N)	35	26	8	69
Psycogenic ED (N)	2	9	3	14
Cavernosal ED (N)	3	3	11	17
Total (N)	40	38	22	100

ED: Erectile Dysfunction

Table 2. *Comparison of PDU results and etiological factors as determined by technique 2*

	Doppler			
Comparison of Step 1 and PDU	Arterial ED	Psycogenic ED	Venous ED	Total
	32	1	2	35
Arterial	6	37	19	62
ED (N)	2	0	1	3
Psycogenic	40	38	22	100

ED: Erectile Dysfunction

Table 3. *Comparison of PDU results and etiological factors as determined by technique 3*

	Doppler			
Comparison of Step 3 and PDU	Arterial ED	Psycogenic ED	Venous ED	Total
Arterial ED (N)	33	1	2	36
Psycogenic ED (N)	3	33	7	43
Cavernosal ED (N)	4	4	13	21
Total (N)	40	38	22	100

ED: Erectile Dysfunction

Diagnostic techniques, such as penile Doppler USG, cavernosometry, follow-up for nocturnal penile tumescence and penile plathysmography typically necessitate specialized, expensive equipment; many of these techniques are additionally rather invasive. Therefore, the majority of these techniques are not readily available in many clinics. For all of these reasons, the etiological factors for ED can be difficult to identify.

After PDE type 5 inhibitors became more commonly and successfully used for the treatment of ED, the search for the underlying etiology of ED has become less of an issue. Even so, it is important to note that the efficacy of some PDE 5 type inhibitors varies for different etiologies of ED[12,13]. However, the efficacy of oral drugs to treat ED differs based on the risk factors or underlying etiologies of ED. Therefore, sufficient knowledge about the underlying etiology of ED in a patient is beneficial before starting the therapy[14].

The IIEF scale is known to demonstrate the degree of ED, but this scale is unable to determine the underlying etiology unless an invasive diagnostic modality is used as an adjunct. Our results using technique 3 of the modified IIEF exhibited similar results as those recovered with PDU in 79% of our patients. This result is consistent with the findings of Hatzichristou et al. who showed that commonly used diagnostic techniques can accurately diagnose approximately 80% of patients[15]. Today, PDU is also considered to be one of the most common techniques for diagnosing ED[16]. On the other hand, the intracavitary agents used in PDU are against the normal physiological mechanisms, by their direct smooth muscle relaxing abilities; PDU accordingly has a low accuracy rate[17].

Even though Tang et al. and Deveci et al. have reported that the simplified IIEF-5 is not a definitive diagnostic tool to discriminate the pathophysiological causes of ED, our data showed that this scale can be used with a modification[18,19]. However, Cordeiro et al. concluded in their study that the IIEF-5 was associated with the diagnosis of coronary artery disease and that its use could add information risk stratification in hypertensive patients[20]. By using the modified IIEF technique, particularly after its third technique, the underlying etiology of ED can be determined in the majority of cases. This scale is accordingly an important asset to urologists.

Although the majority of the techniques to determine the pathogenesis of ED are invasive, the modified IIEF is a simple and accurate technique, particularly after its third technique. This scale is of great use to urologists in their clinical practice.

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OLGU SUNUMU / *CASE REPORT*

A Reason of Delayed Weaning in Critical Care: Amiodarone Pulmonary Toxicity

Yoğun Bakımda Gecikmiş Weaning Nedeni Olarak Amiodaron Pulmoner Toksisitesi

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ABSTRACT

Amiodarone is a frequently used antiarrhythmic drug in critical care which was used to treat especially ventricular arrhythmias. But it must known that secondary to its chemical properties, drug tends to accumulate in tissues and it presents as cardiac, ophtalmic, pulmonary and neurological side effects. Amiodarone pulmonary toxicity (APT) is one of the life-threatening side effects of the drug which may present as respiratory failure. And thorax computed tomography scans demonstrate the pathology with pneumonitis, groung glass opacities and fibrosis. Dispnea and cough are common clinical presentations. But an intubated and mechanically ventilated patient's respiratory failure secondary to APT may reflect as only delayed weaning as in our case. Most importantly, rapid diagnosis and early treatment are the most important factors that reduce the mortality of patients.

Key words: *amiodarone; pulmonary toxicity; critical care*

ÖZET

Amiodaron yoğun bakımda sıkça kullanılan bir antiaritmiktir ve özellikle ventriküler aritmilerin tedavisinde kullanılır. Ama bilinmelidir ki kimyasal yapısından dolayı ilaç dokularda birikebilir ve kardiyak, oftalmik, pulmoner ve nörolojik yan etkiler oluşturabilir. Amiodaron pulmoner toksisitesi (APT) ilacın hayatı tehtit eden yan etkilerinden biridir ve solunum yetmezliği şeklinde karşımıza çıkabilir. Hastalık toraks bilgisayarlı tomografisinde pnömonitis, buzlu cam opasiteleri, fibrosis bulgularını verir. Dispne ve öksürük en sık görülen belirtilerdir. Ancak tıpkı bizim olgumuzda olduğu gibi, entübe ve mekanik ventilasyon uygulanan bir hastada APT'nin yarattığı solunum yetmezliği karşımıza sadece gecikmiş ventilatörden ayrılma olarak çıkabilir. En önemlisi hızlı tanı ve erken başlanan tedavi hastaların mortalitesini azaltan en önemli faktörlerdir.

Anahtar kelimeler: *amiodaron; pulmoner toksisite; yoğun bakım*

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Introduction

Amiodarone is one of the most prescribed antiarrhthmic drug by clinicians. The popularity of the drug comes from its efficacy and extend indications in terms of different types of arrhythmias. But amiodarone has relations with dangerous side effects like amiodarone pulmonary toxicity (APT). The prevalence is estimated to be about 5%. The risk of APT occurance increased by drug dose and therapy duration. Clinical manifestations of APT are; decreased lung capacity, cough, weight loss[1,2]. But in critical care these manifestations may be masked and clinician must be aware of APT, whether the patient used high dose of amiodarone. In this case report we present a delayed weaning according to APT with it's clinical presentation, diagnosis and successful therapy.

Case

65-year-old female patient with hypertension, diabetes and chronic obstructive pulmonary disease, obesity (BMI >35 kg/m^2) referred to the hospital with respiratory failure. Acute coronary syndrome was detected and percutan coronary angiography was performed. During the procedure two clogged coronary arteries opened successfully. Secondary to unstable haemodynamic measurements patient transferred to our critical care service. After the physical and laboratry examination, atrial fibrillation, significant respiratory failure secondary to pulmonary edema and pneumonia, impaired renal functions secondary to contrast induced nephropathy were detected additionally to the acute coronary syndrome. Patients glasgow coma scale was 14 at the application to the critical care. Secondary to respiratory failure supportive noninvasive mechanical ventilation started. Hemodialysis was performed for deep metabolic acidosis secondary

to renal impairment. Antibiotic therapy for pneumonia and other recommended drugs (acetylsalicilic acid 1x100 mg/day, clopidogrel 1x75 mg/day, metoprolol 1x50 mg/day) by cardiologists were started. At the 4th day of the critical care cardiac arrest occurred secondary to malignant ventricular arrhthmias. Three times cardioversion was performed with successful resuscitation. Patient started to receive per oral amiodarone (2x200 mg/day) therapy. At the 7th day of the critical care malignant arrhythmais reappeared and cardioversion was performed again. The amiodarone dose concluded insufficient and it increased to 3x200 mg/per day. From the fourth day of the process patients was still intubated and mechanically ventilated. Hemodialysis therapy was still continue every two days. Cardiac rithm of the patient stabilized. After a few days pneumonia was deteriorated, volume load on lungs depleted and weaning planned. Intermittent chest x-rays showed new patchy infiltrates. Patient was searched in terms of new pneumonia or pleural edema, pulmonary thromboemboli, but all markers of these diseases were negative. But patient could not wean. Clinicians concluded APT secondary to patchy infiltrations in chest x-ray, respiratory failure without any other reasons and high dose amiodarone medication and thorax computed tomography was performed. Bilateral ground glass opacities, significant parahiler opacities, bronchovascular irregularities, pleural and paranchimal fibrosis, small pleural effusions were detected (Figure 1). All these clinical and radiologic findings inclined clinicians to the APT. After the diagnosis, amiodarone was stopped and 50 mg/day methylprednisolone was started. Patient's respiratory functions started to improve 5 days after the steroid therapy and patient weaned at the 9th day of the APT diagnosis. After weaning, improvement of the patient got faster. She mobilized better, oral intake increased, did not need supportive oxygen therapy and she was discharged from critical care to the ward at the 3rd day of the extubation.

Discussion

The main indication of amiodarone is suppression of ventricular arrhythmias. Additionally amiodarone can maintain sinus rhythm in patients with atrail arrhythmias[3,4]. So it is a world wide used antiarrhythmic drug with its toxic side effects. Amiodarone is an iodine containing pruduct. In addition, inhibition of thyroxine deiodination to triiodothyroxine may contribute to its antiarrhythmic efficacy. An important property of amiodarone is its high lipid solubility[1]. These properties cause the accumulation of the drug to the tissues like

Figure 1. *Bilateral ground glass opacities, significant parahiler opacities, bronchovascular irregularities, preural and paranchimal fibrosis, small pleural effusions were seen in thorax CT of the patient.*

fat, liver, spleen and lungs. The most serious one is pulmonary toxicity. Pulmonary toxicity risk correlates by plasma amiodarone concentration. Although toxicity may occur in any time or dose of the therapy but more than the dose of 400 mg/day or theraphy of more than two months caused highest risks of pulmonary toxicity, a lower dose, commonly 200 mg daily, for more than two years[5]. Male gender and pre-existing lung disease are potential risk factors of the toxicity. Additionally it was concluded that supplemental oxygen therapy, thoracic or non-thoracic surgery and mechanical ventilation may potentiate the toxicity[6–8]. Even our patient was female the supportive moderate oxygen therapy and mechanical ventilation might potentiate APT. The risk of developing amiodarone-induced pulmonary toxicity may increase with age and an abnormal chest xray or poor pulmonary reserve before treatment with amiodarone[9].

APT pathophysiology consist of direct cytotoxic T cell damage or indirect immunologic damage.[9] Secondary to these mechanisms, finding cytotoxic T cells with bronchoalveolar lavage (BAL) is an one of diagnosis method. Accumulated concentrations of amiodarone derivative in specific lung compartments, such as the type II pneumocyte, further exaggerate this effect[10].

The most common clinical manifestation is interstitial pneumonitis with a subacute onset[1]. Shortness of breath, nonproductive cough, malaise, chest pain are the common clinical presentations.[6] But these findings may not be clarified in an intubated critical care patient. As our case report delayed weaning process may be the only presentation. With this aspect, the patient's weaning delayed, the dose of oxygen concentration could nor decreased and newer patchy infiltrates occured in chest x-ray. And the other reasons of this presentation like infectious pneumonia etc were excluded with BAL culture and other infection markers. Especially clinicians must be suspicious of APT in terms of respiratory impairments whether a critical care patient received high doses of amiodarone (our patient received 600 mg per day) with respiratory supportive therapy.

There are no symptoms for the diagnosis of APT. New infiltrates on chest x-ray, reduced diffusion capacity in the DLCO, restrictive or mixt type pulmonary function test results, evidence of the immune response with BAL are the diagnostic methods of APT. Interstitial, alveolar or mixt infiltrates, ground glass opacities, pleural thickening, pulmonary fibrosis are the signs of the APT[10,11]. In our case, bilateral ground glass opacifications, pleuroparanchimal fibrosis were detected as mentioned in previous literature.

After APT diagnosis, cessation of the drug and systemic corticosteroid therapy were recommended. It must known that amiodarone has long elimination half life and the clinical improvements may be delayed. Recurrences have been described up to 8 months after amiodarone withdrawal. Amiodarone induced fibrosis is irreversible and respondent to treatment with corticosteroid drugs[11]. In our patient significant clinical improvements were recorded on the 10th day of the drug cessation. Prednisone therapy is recommended in doses of 40–60 mg/day orally[1]. We used 50 mg/day methylprednisolone after the diagnosis and patients may weaned secondary to pulmonary resolution.

The prognosis of APT is usually positive. Mortality in amiodarone pneumonitis ranges between 21% and 33% of patients who are treated in hospital[11].

There are numerous reports about APT but less of them from critical care. Intensive care givers must be aware of APT because being intubated and mechanically ventilated and other frequent critical care disorders like pneumonia, pulmonary thromboemboli may mask the diagnosis. It was known that prompt diagnosis, early cessation of amiodarone and steroids increase the survival rate as happens in our case.

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OLGU SUNUMU / *CASE REPORT*

Bortezomib Induced Congestive Cardiac Failure in a Patient with Multiple Myeloma

Multipl Myelomalı Bir Hastada Bortezomib İlişkili Konjestif Kalp Yetmezliği

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ABSTRACT

Bortezomib is a proteasome inhibitor commonly used for the treatment of multiple myeloma, and it has some cardiac side effects. The incidence of cardiac failure associated with bortezomib therapy in clinical trials remains incidental. We describe a 82-year-old patient with International Staging System Stage III multiple myeloma. Combined chemotherapy with bortezomib 1.3 mg/m² on days 1, 8, 15, 22 of each cycle and 40 mg/day dexamethasone (days 1 to 4) was started to him. Two days after the end of the 3rd cycle of chemotherapy (12th dose of bortezomib), he admitted with mild edema of bilateral lower extremity. Echocardiography revealed a drop in the left ventricular ejection fraction from pretreatment levels of >55% to 30–35%. Therefore; bortezomib treatment was postponed and he was treated for congestive heart failure. The patient's symptoms improved and the ejection fraction normalized after three months following discontinuation of bortezomib.

Key words: *bortezomib; congestive heart failure; multiple myeloma*

ÖZET

Bortezomib genellikle multipl myeloma tedavisi için kullanılan bir proteazom inhibitörüdür ve bazı kardiyak yan etkilere sahiptir. Klinik çalışmalardaki bortezomib tedavisiyle ilişkili kalp yetmezliği insidansı tesadüfi olarak kalır. Biz Uluslararası skorlama sistemine göre Evre 3 multipl myeloması olan 82 yaşında bir hastayı sunuyoruz. Bu hastaya kombine kemoterapi (her bir siklusta bortezomib 1,3 mg/m² D1, D8, D15, D22 ve 40 mg/gün deksametazon [D1–4]) başlandı. Kemoterapisinin 3 siklusunun tamamlanmasından 2 gün sonra (bortezomib tedavisinin 12. dozu) hasta bilateral alt extremitelerde hafif ödem nedeniyle başvurdu. Ekokardiyografide ejeksiyon fraksiyonun tedavi öncesi >%55'den %30–35'e düştüğünü gösterdi. Bu nedenle bortezomib tedavisi kesildi ve konjestif kalp yetmezliği için hasta tedavi edildi. Bortezomib kesilmesinden 3 ay sonra hastanın klinik semptomları düzeldi ve ejeksiyon fraksiyonu normale döndü.

Anahtar kelimeler: *bortezomib; konjestif kalp yetmezliği; multipl myeloma*

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Introduction

Bortezomib is an antineoplastic drug which was originally synthesized in 1995. Firstly, the drug was tested in a small phase I clinical trial on patients with multiple myeloma, and the treatment with bortezomib was approved for initial treatments of patients with Multiple Myeloma by the Food and Drug Administration (FDA) in 2008. Also, the bortezomib was approved for the treatments of non-Hodgkin lymphoma, Waldenström's macroglobulinemia, and systemic light chain amyloidosis, among others by FDA.

It was documented that bortezomib has several side effects that necessitates abruption or sometimes cessation of the therapy. It is associated with peripheral neuropathy in 30% of patients; occasionally, it can be painful. In addition, myelosupression causing neutropenia and thrombocytopenia can also exist and be dose-limiting. Another side effect of Bortezomib is shingles, but this problem can be prevented with prophylaxis of acyclovir[1]. Gastro-intestinal effects and asthenia are the most common adverse events[2]. The incidence of cardiac failure or other cardiovascular effects associated with bortezomib remains incidental. Herein, we present the case of an 82-year-old male patient who devoloped temporary heart failure secondary to bortezomib based chemotherapy because of rarity.

Case

A 82 year-old male patient admitted to our clinic with pain on his back and weakness. He had no prior cardiac history and no additional risk factor except from his age for cardiac disease. On evaluation of his routine laboratory tests, he was found to have haemoglobin of 8.7 g/dl, haematocrit of 26.6%, white blood

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cell (WBC) count of 10.200/mm^3 and platelet count of 148000 μ/l. Level of serum urea was 67 mg/dl, creatinine 3 mg/dl, sodium 129 mEq/L, potassium 4.46 mEq/L, uric acid 11.7 mg/dl, total protein 9.5 mg/dl, albumin 2.8 mg/dl, aspartate aminotransferase 27 UI/L, alanine aminotransferase 13 UI/L, gamma glutamyl transferase 14 U/L, IgG 44.05 g/L, IgA 0.26 g/L, IgM 0.19 g/L. Tests of thyroid function was normal. Diffuse osteopenia confirmed with the graphies of bone survey. Due to the presence of severe anemia and osteopenia, diagnosis of multiple myeloma was considered. Monoclonal protein band was examined by the use of serum protein electrophoresis and the immunofixation electrophoresis showed monoclonal immunogobulin bands of IgG-Kappa. The level of beta-2 microglobulin was 7.49. Bone marrow aspiration and biopsy confirmed to the diagnosis of International Staging System stage III multiple myeloma. Electrocardiography was normal and transthoracic echocardiography revealed a left ventricular EF value of this patient >55% by modified Simpson method.

The patient treated with three cycles of bortezomib 1.3 mg/m^2 on days 1, 8, 15, 22 of each cycle and 40 mg/day dexamethasone (days 1 to 4). With the bortezomib based chemotherapy the level of creatinine decreased to its normal ranges in our patient. However, two days after the end of third cycle of therapy the patient reported that he has an increase on fatigue, mild dyspnea and mild edema of lower extremity. He did not experience any chest pain or myalgia. Pulmonary auscultation revealed crepitation of bilateral basillar region of the lungs in physical examination. Bilateral mild edema was present from the dorsalis pedis to the ankles. ECG did not show any signs of ischemia. The chest X-Ray graphy showed an increased heart-chest ratio. Thus, the patient consulted with cardiologists. The serum levels of cardiac enzymes (creatinine kinase-MB, troponin) were in normal ranges. Echocardiography was applied to the patient by same cardiologist and global hypokinesia was confirmed. Ejection fraction was estimated to be 30–35% by modified Simpson method. Coronery anjiography was not performed because the patient did not gived informed consent. Therefore, Bortezomib based chemotherapy was terminated. The anti-myeloma treatment of this patient was reconstituted to melphalan and prednisolone. The patient was treated for congestive heart failure with diuretics, angiotensin-converting enzyme inhibitors and beta blockers. The patient responded well to this treatment. The ejection fraction and global hypokinesia normalized after three months.

Discussion

Bortezomib, a dipeptidyl boronic acid, is selective and reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of ubiquitylated proteins. Inhibition of the ubiquitin-proteasome system has been shown to lead to hyperubiquitination of intracellular proteins[3]. It may prevent degradation of pro-apoptotic factors and inhibition results in the increase of apoptosis[4]. Bortezomib, by inhibiting ubiquitin-proteasome pathway, would lead to accumulation of ubiquitinated proteins in cardiac myocytes[5]. None of necrotic or apoptotic cells are found in histopathological heart examination and no rise in troponin I levels[6].

Orciuolo et al. reported 8 cases (11.6%) with cardiotoxicity ranging from heart failure to arrhythmias in 69 cases[7]. The APEX trial reported seven patients who developed congestive heart failure. In this study, the incidence of congestive cardiac failure was 2% in both bortezomib and high dose dexamethasone group. In the SUMMIT and CREST trials, the incidence of cardiac failure associated with bortezomib therapy was very low. Most of the cases used other chemotherapeutic agents including cardiotoxic anthracyclines in the trials. In a phase III study using bortezomib as a first line agent combined with melphalan and prednisone, no incidence of cardiomyopathy was documented[8]. The incidence of cardiotoxicity that associated with treatment of bortezomib ranges from 0% to 5% in various studies[9].

Up to now; very few cases with heart failure that associated with bortezomib treatment have been reported in the literature[10]. In our patient; baseline left ventricular function was normal. Heart failure devoloped after bortezomib-based treatment (total 15.6 mg/m^2). Cumulative dose of the drug administered to patient ranged from 0.7 mg/m^2 to 31.2 mg/m^2 in the literature. All cases showed improvement in left ventricular ejection fraction following discontinuation of bortezomib in the literature. The ejection fraction returned to normal after three months following discontinuation of bortezomib in our case similarly with the literature.

Congestive heart failure is rarely occured important toxicity associated with treatment of bortezomib. Patients with history of cardiac diseases or use of anthracycline drugs may be at increased risk for bortezomib related congestive heart failure. Therefore, we recommend close monitoring of the cardiac parameters in patients undergoing this therapy.

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OLGU SUNUMU / *CASE REPORT*

Multiple Mucoceles Located in the Nasopharynx and Hypopharynx: Case Report

Nazofarenks ve Hipofarenks Yerleşimli Multipl Mukosel: Olgu Sunumu

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ABSTRACT

Mucoceles are asymptomatic masses generally located intraorally, that can occur in various diameters and dimensions. In majority of the cases, they are single, but can be rarely multiple. In this case presentation, a very rare case of minor salivary gland mucoceles in a 45-year-old female patient, in the left ariepiglottic fold of the hypopharynx and in the left rosenmüller fossa of the nasopharynx, has been discussed with regard to the diagnosis and treatment in the light of the literature.

Key words: *mucocele; salivary gland; Rosenmüller fossa; aryepiglottic fold*

ÖZET

Mukoseller değişik çap ve boyutlarda olabilen, genellikle intraoral yerleşimli asemptomatik kitlelerdir. Çoğunlukla tektir ancak ender de olsa multipl olabilmektedir. Bu olgu sunumunda kırk beş yaşında bayan hastada, oldukça ender olan nazofarenkste sol rosenmüller fossa ve hipofarenkste sol ariepiglottik foldda minör tükürük bezi mukoseli olgusu tanı ve tedavisi literatür eşliğinde tartışıldı.

Anahtar kelimeler: *mukosel; tükürük bezi; Rosenmüller fossa; aryepiglottik fold*

Introduction

Mucoceles are benign cystic lesions of the salivary glands that can be various diameters and dimensions, can be located superficially or deep, and can be of blue-purple or normal mucosal colour. Although they can be encountered in all places where salivary glands are located, in general they can be observed in the intraoral region, the lateral of the midline in the lower lip, and on the buccal or palatinal mucosa[1,2]. Mucoceles are usually single, but they might rarely be multiple[2]. The treatment of salivary gland mucocele is surgical excision[3].

In this report, with regard to the diagnosis and treatment, we aimed to share our case in whom there was symptomatic multiple mucoceles in a minor salivary gland, which were localized in the nasopharynx in the left rosenmüller fossa and in the aryepiglottic fold in the hypopharynx, which is very rarely encountered.

Case

A 45-year-old female patient presented to our clinic with the complaints of intermittent difficult breathing through the left side of the nose and the feeling of food getting stuck in the throat during swallowing, which had been presented for one year. The physical examination performed on the patient revealed normal findings, and on the endoscopic examination of the nasopharynx and the larynx, a cystic mass was observed in the nasopharynx filling the left rosenmüller fossa and in the left aryepiglottic fold neighboring the epiglottis (Figure 1, 2). The laboratory findings were normal and the patient's past medical history was unremarkable.

Under general anaesthesia, using the endoscopic method, the cystic mass filling the left rosenmüller fossa in the nasopharynx was marsupialized, and in laryngoscopy, the cystic mass in the left aryepiglottic fold neighboring the epiglottis was totoally excised under microscopy. The pathology of the excision material was reported as a salivary gland mucocele (Figure 3). No recurrence was observed on the follow-ups performed for two years.

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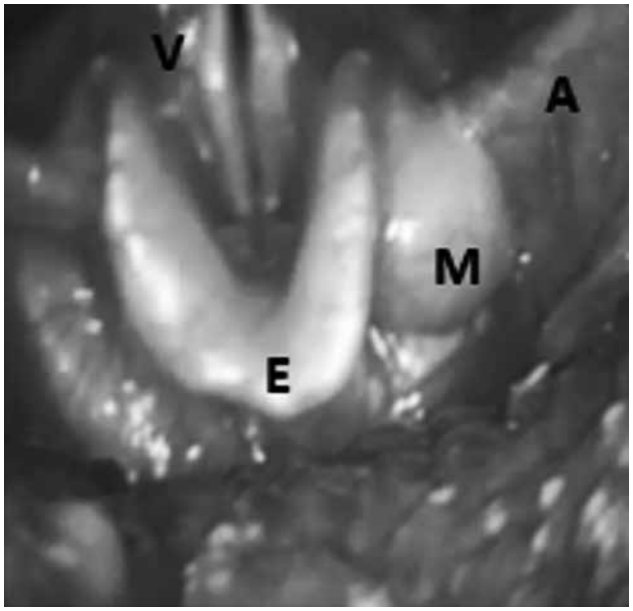

Figure 1. *Laryngeal Endoscopic Image (V; vocal cord, A; left aryepiglottic fold, E; epiglottis, M; mucoceles).*

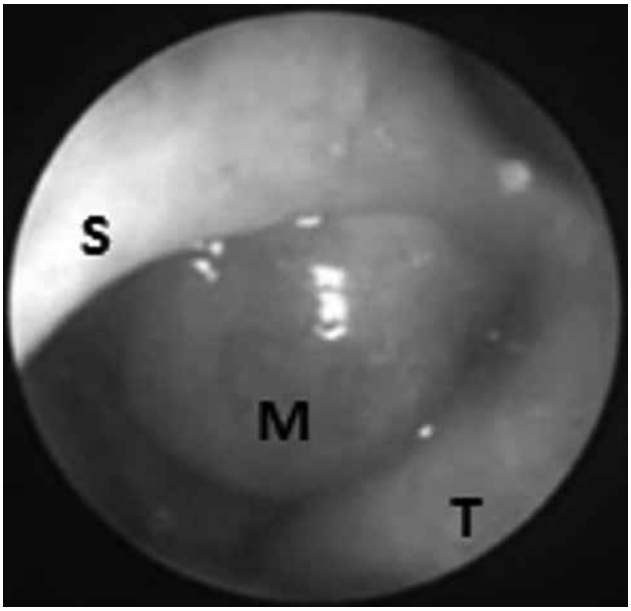

Figure 2. *Nasopharyngeal Endoscopic Image (S; septum, T; left torus tubarius, M; mucoceles).*

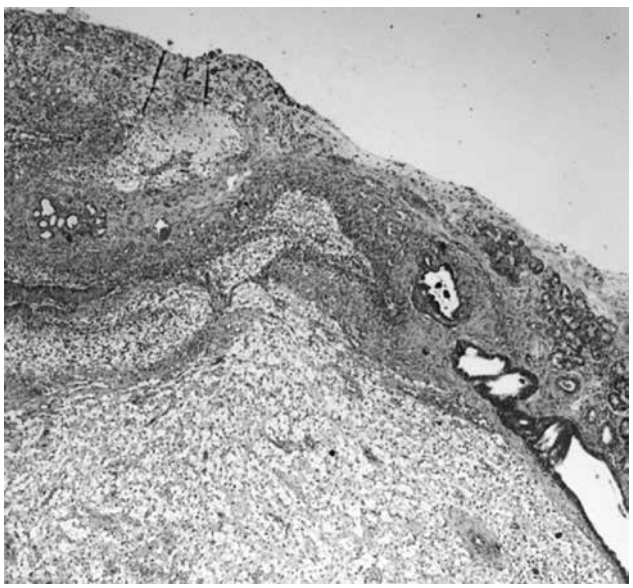

Figure 3. *Minor salivary gland mucocele. (40 x hematoxylin/eosin).*

Discussion

Mucocelles, the word meaning of "cavity filled with mucus", are frequently observed soft tissue lesions of the oral cavity[1]. More than 70% of mucoceles originate from minor salivary glands, and in the order of decreasing frequency, mucoceles are localized in the lower lip, in the cheek, at the base of the mouth, at the palate and on the tongue, but mucoceles can be seen in all places in which there is a salivary gland[4,]Clinically, they are painless asymptomatic lesions, which demonstrate fluctuations, and which generally occur in single form, although they can rarely be multiple in numbers[1,5]. In our case, there were multiple minor salivary gland mucoceles causing symptoms, located in the nasopharynx, filling the left rosenmüller fossa and on the left aryepiglottic fold in the hypopharynx neighboring the epiglottis, which is a very rare situation.

Common etiological factors effective in the formation of mucoceles are trauma, chronic biting and smoking, but they can also appear due to other etiological factors. In particular of the autoimmune diseases, Sjögren Syndrome has been reported to be closely related with development of mucocele[6,7]. In our case, the patient underwent evaluation with regard to autoimmune diseases and no findings consistent with autoimmune diseases was observed. There was no history of use of irritative substances or trauma in our patient.

The diagnosis of mucoceles is generally made clinically; however, the definitive diagnosis is made through histopathological assessment. Lipoma, lymphoepithelial cysts, lymphangioma, and mucoepidermoid carcinoma should be considered in the differential diagnosis[1]. In our case, the diagnosis of salivary gland mucosele was made through histopathological evaluation of the mass.

The treatment of mucocele is surgical and the surgical method is determined according to the localization, size and its proximity to other anatomical structures. Small sized mucoceles are excised together with the related minor salivary glands[1,3,8]. Mid-sized mucoceles are dissected and removed, and larger mucoceles and mucoceles close to anatomical structures undergo marsupialization[1,3]. In our case, due to the difficulty in access to the mucocele in the nasopharynx that had filled the left rosenmüller fossa, it was marsupialized through the endoscopic method, and the mucocele on the aryepiglottic fold in the hypopharynx neighboring the epiglottis was totally excised through direct laryngoscopy using a microscope. No recurrence was observed in the 2-year follow-ups of the patient.

Mucocele should be considered in the differential diagnosis of masses developing in the area of salivary glands, and the patient in whom the diagnosis of a mucocele is made, should undergo evaluation with regard to autoimmune diseases. Due to the fact that the mucoceles may ocur in multiple numbers, although rare, we suggest that patients diagnosed with mucocele should be evaluated through endoscopic imaging methods.

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DERLEME / *REVIEW*

The Effects of Helicobacter Pylori Infection on Nutrition Status and Metabolism

Helicobacter Pylori Enfeksiyonunun Beslenme Durumu ve Metabolizma Üzerine Etkileri

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ABSTRACT

H.pylori infection, which is common in the world as well as in our country and has been identified as a group 1 carcinogen by the World Health Organization (WHO) is a Gram negative pathogen. Low socio-economic level, low consumption of fruits and fresh vegetables, increased consumption of fast food, tobacco use and poor oral hygiene are reported risk factors for H.pylori infection. It is considered that distruption of the absorption of some micronutrients affected the appetite and food intake because of due to changing ghrelin and leptin hormone levels in the presence of H.pylori. Also, some studies showed that H.pylori infection is effective in the development or progression of gastrointestinal diseases, metabolic syndrome, insulin resistance, diabetes and diabetes complications. Some foodstuffs and nutrients are thought to have infection-protective and/or having preventive effects and recent studies have focused on these subject. It is mentioned that especially fresh fruits, vegetables and some probiotic formulation can play an important role in the treatment of H.pylori infection. The relationship between nutrition and H.pylori infection and its metabolic effects of H.pylori will be discussed in this review.

Key words: *Helicobacter pylori; ghrelin; appetite; nutrition; nutrients*

ÖZET

H.pylori ülkemizde ve dünyada yaygın olarak görülen ve Dünya Sağlık Örgütü (DSÖ) tarafından 1. sınıf karsinojen olarak tanımlanan Gram negatif bir patojendir. Düşük sosyo ekonomik düzey, taze sebze, meyve tüketiminin az ve fast food tüketiminin fazla olması, yetersiz ağız hijyeni ve sigara kullanımının H.pylori enfeksiyonuna yakalanma riskini arttırdığı bildirilmektedir. H.pylori varlığında ghrelin ve leptin hormonlarının seviyelerindeki değişiklik nedeniyle iştah ve besin alımını etkilemekte, bazı mikro besin öğelerinin emilimini bozmaktadır. Ayrıca yapılan çalışmalarda gastrointestinal sistem hastalıkları, metabolik sendrom, insülin direnci, diyabet ve diyabetin komplikasyonlarının gelişimi veya ilerlemesinde H.pylori enfeksiyonunun etkili olduğu gösterilmektedir. H.pylori enfeksiyonunda bazı besinlerin ve besin öğelerinin koruyucu ve/veya önleyici etki gösterdiği düşünülmekte ve bu konuda yapılan çalışmaların sayısı her geçen gün artmaktadır. Özellikle taze meyve, sebzeler ve bazı probiyotik formülaların H.pylori enfeksiyonu tedavisinde önemli rol oynadığından bahsedilmektedir. Bu derlemede de H.pylori enfeksiyonunun beslenme durumu ile ilişkisi ve metabolizma üzerine etkileri irdelenecektir.

Anahtar kelimeler: *Helicobacter pylori; ghrelin; iştah; beslenme; besin öğesi*

Introduction

Known as a Gram negative pathogen, *H.pylori,* which is common in the world as well as in our country, affects more than about 50% of population[1]. More than 80% of the population in developing countries and 20–80% in developed countries suffers from this bacteria and its effects[2]. In Turkey, the frequency of *H.pylori* infection have reported to be approximately 70–80% according to the recent studies[3,4]. Urea breath test, stool antigen scanning and endoscopic evaluation is used in the diagnosis of *H.pylori* infection[5]. The incidence of infection has been increasing with age since the early years and those who have lived under poor socioeconomic conditions especially in childhood are at a more risk of *H.pylori* infection in the following years[6]. Low socioeconomic status, low consumption of fresh vegetables and fruits, increased fast food consumption, poor oral hygiene and tobacco use are known as risk factors for *H.pylori* infection[3,4,7–10] as well as alcohol use but, present data are contradictory[9,11].

H.pylori, identified as a group 1 carcinogen by the WHO plays an important role especially in the development of gastric cancer and mucosal-associated lymphoid tissue lymphoma[5]. *H.pylori* colonize in the epithelial cell lining of the stomach by affecting the human gastric flora that disrupts the gastric mucosal integrity. The presence of bacteria affect the levels of ghrelin and leptin hormones results in negative effects on appetite and food intake[12]. Some micronutrient malabsorptions, especially folate,

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homocysteine and iron deficiency can develop in the presence of *H.pylori* infection[2].

Specific foods and nutrients have protective and/or preventive effects in the development or progession of the infection. Especially fresh vegetables and fruits can play an important role in the treatment of *H.pylori* infection[5]. Honey and green/black tea consumption has also been shown to be associated with reduced prevelance of *H.pylori* infection[13].

H.pylori infection has an important role in terms of public health because of its worlwide distribution and high level of prevalence and the importance of associated pathologies according with gastroduodenal diseases[14]. Besides the gastrointestinal diseases, *H.pylori* can be associated with diabetes and development of diabetic complications, metabolic syndrome and insulin resistance also[15]. So, this paper aims to discuss the relationship between nutrition and H.pylori infection and its metabolic effects of *H.pylori*.

Pathophysiology of H.pylori and Its Effect on Appetite

H.pylori colonizes in the gastric epithelium and has an important urease activity that leads to the production of ammonia in order to protect itself from gastric acidity. It also produces enzymes such as glicosulfatase, phospholipase A2 and C, which play an important role in the development of gastric mucosal damage. *H.pylori* leads to an inflammatory response through the gastric epithelium with the production of proinflammatory cytokines such as interleukin 8 and interleukin 1β[2]. *H.pylori* has various virulence factors that play an important role in the pathogenesis of infection. Especially vacuolating toxin A (Vac-A) and cytotoxin-associated gene A (Cag-A) positive are associated with greater pathogenicity and more severe disease[2,14]. CagA positive strains cause a stronger inflammatory response of gastric mucosa with increasing of proinflammatory cytokines. On the other hand, the VacA gene is responsible for vacuolization and apoptosis of gastric epithelial cells. *H.pylori* infection reduces the gastrointestinal hormones and the absorption or bioavailability of essential nutrients and *H.pylori* is associated with metabolic balance also. Additionally, *H.pylori* infection plays a role in changing ghrelin and leptin levels[2].

Ghrelin peptide is constituted of 28 amino acids with a fatty acid chain modification (octanoyl group) on the third amino acid. Ghrelin peptide was originally isolated from the stomach, but ghrelin protein has also been identified in other peripheral tissues. The acylated forms of ghrelin have been recognised as the major active orexigenic molecules regulating energy balance. When studying the effects of ghrelin on energy balance, differential influences of the acylated and non-acylated forms of the peptide must be considered[16,17]. While active form of ghrelin regulates growth hormone-releasing and food intake, inactive form of ghrelin is effective on cell proliferation and adipogenesis. Acylated ghrelin increases the food intake and involves in positive energy balance. On the other hand, des-acylated ghrelin decreases food intake and devoid of any endocrine activities[18,19].

The presence of *H.pylori* on the gastric mucosa affect the levels of ghrelin and leptin hormones results in negative effects on appetite and food intake. Leptin concentrations were higher, ghrelin concentrations and ghrelin/obestatin ratios were lower in the *H.pylori*-positive group than in the *H.pylori*-negative group. Additionally, appetite was decreased in *H.pylori* positive group[12,20]. After the eradication of *H.pylori,* ghrelin levels and appetite was increased that results in body weight gain[21,22]. Ghrelin levels and body mass index (BMI) was lower in *H.pylori* positive group than *H.pylori* negative group in older ages and *H.pylori* infection may be one of the underlying causes of malnutrition in the elderly[23].

The relationship between *H.pylori* infection and gastric hormones has also been investigated. The effect of *H.pylori* on ghrelin production has been associated with *H.pylori* virulence. The extent of gastric damage and level of the infection has been thought to play a key role in the modulation of ghrelin levels. Increased leptin and gastrin levels, decreased plasma ghrelin levels and a negative effect on appetite and dyspeptic symptoms were found to be the consequences of gastric mucosal damage due to *H.pylori*[2].

H. Pylori and Absorption Disorders

H.pylori in the gastric mucosa can cause a malabsorption of certain vitamins and minerals. In several studies, vitamin B_{12} and folate deficiency was found in *H.pylori* positive patients compared with healthy individuals[2,24,25]. Reduction of gastric acid secretion, deficiency of ascorbic acid and blocking of iron binding protein lead to iron deficiency in patients with *H.pylori*[26]. Iron deficiency and anemia were seen more frequently especially in children[27,28]. Hypochlorhydria (reduction of HCL production in stomach) decreases iron absorption by reducing the availability of ascorbic acid. So that, it decreases the absoption of non-heme

iron leading to the reduction in the transformation of ferric to ferrous form and using iron by *H.pylori* strains as a growth factor in patients with *H.pylori*. It may be the main reason for iron deficiency[2]. Absorbtion can be decreased due to the change in gastric physiology[29]. Also, the increase in gastric pH reduces the iron solubility and iron absorbtion will be affected by reducing the bioavailability of vitamin B_{12} and folic acid[30].

The presence of *H.pylori* on the gastric mucosa affect the levels of vitamin C. Induced by *H.pylori*, chronic gastritis may be associated with hypochlorhydria and accompanied by low levels of vitamin C in plasma and gastric juice both in adults and children. Vitamin C levels in whole blood, plasma and the gastric juice pH in Korean children are closely related to the severity of *H.pylori* infection and the histologic changes in the stomach[31]. High concentration of vitamin C in gastric juice might inactivate *H.pylori* urease, the key enzyme for the pathogen's survival and colonization into acidic stomach. Moreover higher prevalence of *H.pylori* infection is related with low serum Vitamin C levels and gastric juice[29,32].

Vitamin B_{12} deficiency due to food-cobalamin malabsorption is associated with gastritis originating from *H.pylori*. Decreased secretion of intrinsic factor by parietal cells may be the probable cause of cobalamin malabsorption and atrophic gastritis secondary to *H. Pylori* infection is one explanation for vitamin B_{12} malabsorption. Low acid-pepsin secretion results in decreased release of free vitamin B_{12} from food proteins and/or promotes overgrowth of bacteria that bind vitamin B_{12} for their own use in the hypochlorhydric stomach and small intestine[33,34]. In a study, *H.pylori* was detected in 56% of 138 patients with vitamin B_{12} deficiency and eradication of *H.pylori* infection successfully improved anemia and serum vitamin B_{12} levels in 40% of 77 infected patients[35].

There is a concern about the relationship between β-carotene bioavailability and *H.pylori* infection. In the presence of *H.pylori*, hypochlorhydria and achlorhydria significantly decreased β-carotene bioavalability[36]. *H.pylori* infection and low β-carotene in plasma contribute to the increased risk of gastric atrophy, indicating that *H.pylori* infection might be associated with low plasma β-carotene[37].

Effects of Nutrition on the Prevention and Eradication of H. Pylori Infection

Some nutritional regimens may reduce the virulence of *H.pylori* infection. Some food items like fruits and vegetables, special spices, bee products (e.g. honey and propolis) and probiotics are supposed to have positive health impacts[5]. Fruits and vegetables have been mentioned as anti *H.pylori* agents according to their content of antioxidant compounds like bioflavonoids, phytochemicals and ascorbic acid as well as honey, which is known to have antimicrobial activity due to its hydrogen peroxide and non-peroxide components. Also, green tea has positive effects on the prevention of *H.pylori* due to its polyphenolic catechins content[5]. Additionally, tea catechins may have antibacterial effects against *H.pylori* and therapeutic effects against gastric mucosal injury[38]. Foods/drinks containing polyphenols such as red wine and green tea have an inhibiting effect on the urease activity of *H.pylori* and thus being effective on mitigating the related symptoms[39]. There was a positive corelation between daily consumption of sausage, mayonnaise, soft drinks and burgers with the incidence of *H.pylori* infection. Lower consumption of fresh fruits and vegetables are an important risk factor for the development of *H.pylori* infection. In addition, fish, honey, olive oil, peans and beans are suggested to have negatively correlation with *H.pylori* infection[8].

Increased salt consumption is a risk factor for gastric cancer and associated with *H.pylori*. *H.pylori* infected individuals with a higher salt consumption had a risk of early gastric cancer 10 fold more than *H.pylori* negative individuals with a low salt consumption, and the consumption of fruits and vegetables reduced the risk of gastric cancer[40].

Milk and dairy products are another food items supposed to have protective effects against *H.pylori* infection and may support the treatment. Especially fermented milk-based probiotics, bovine lactoferrin, immunoglobulin-enriched α-lactalbumin and whey protein have been shown to have beneficial effects on the treatment of *H.pylori*[5,41]. Because of limited data on the benefits of milk and dairy products on *H.pylori*, further studies should be performed to determine the optimal dose and duration of these food items providing clinically useful effects.

Recent studies have focused on broccoli sprouts, manuka honey, blackcurrant oil and omega-3 oil. Isothiocyanate-rich broccoli sprout was found the most effective food against *H.pylori.* Additionally, the broccoli sprouts are most effective when used alone it has sinergetic effect with omega-3 or manuka honey[42,43]. Also, these nutrients may decrease inflammation related to *H.pylori* by blocking the release of IL-8 from gastric epithelial cells[43]. The

bacteriostatic effects of isothiocyanate sulphoraphane (SF), an abundant compound in broccoli sprouts, have been explained by two probable mechanism, a direct effect on *H.pylori* and an indirect effect by triggering the cytoprotective response[39].

Probiotics are defined as 'live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host'. Using probiotics in the treatment of *H.pylori* can reduce the side effects and using probiotics more than two week and including lactobacillus significantly enhanced the efficacy of the eradication[44]. Probiotics have shown their positive effects via maintaining gastric mucosal barrier and acidity and providing protection against the harmful effects of *H.pylori* infection. In addition, probiotics provide a better compliance the treatment as a result of reduced side effects to the intestines[45]. Mechanisms explaining the effects of probiotics on *H.pylori* are described as; competing against *H.pylori* on the gastric mucosal epithelium, providing the production of anti *H.pylori* substances such as acetic acid, propionic acid and butyric acid, supporting the regulation of immune functions and immunoglobulin-A secretion to improve mucosal defensive ability and strengthening the bonds between epithelial cells[44]. Although probiotics have beneficial effects on *H.pylori*, the impacts on *H.pylori* eradication are still controversial due to insufficient data on the effctive certain strain and dosage of probiotics[46].

Nutritional Status After the Eradication of H.pylori

There are some alterations in gastric hormone levels after the treatment of *H.pylori*. After the eradication therapy, appetite and body weight had increased due to the elevation of plasma ghrelin[47,48]. Eradication therapy of *H.pylori* is associated with increased ghrelin levels and growth in children with *H.pylori* positive[49].

After the treatment of *H.pylori*, there are some changes in the blood lipid levels. After the treatment of *H.pylori* infection, body weight and serum levels of total cholesterol, total protein and albumin had significantly increased. Also reported that incidence of hyperlipidaemia significantly increased and pancreatic function significantly improved[50].

Some micronutrient malabsorptions improved after the eradication. Eradication therapy with iron supplementation has been found to be better than using only iron supplementation to provide a significant increase serum iron, serum ferritin and hemoglobin levels in *H.pylori* positive patient with iron deficiency anemia[51]. Also, eradication therapy with iron and folic acid supplementation resulted better than only iron and folic acid supplementation among *H.pylori* infected pregnant women with IDA[52]. Additionally, *H.pylori* infection is associated with IDA and after eradication of *H.pylori* is followed by increasing of serum ferritin and hemoglobin levels in adolescent girls[53]. In a study, evaluated the efects in homocysteine and cobalamin levels after the eradication of *H.pylori,* was found that eradication therapy associated with increasing of cobalamin levels and decreasing of homocysteine blood levels in elderly patients with cobalamin deficiency[54]. Eradication of *H.pylori* is effective also in the absorption of vitamin B_{12}[55].

Relationships With Other Diseases of H.Pylori Infection

H.pylori infection is related with chronic gastritis, peptic ulcer, development of gastric cancer. Also, complications of gastrointestinal diseases. *H.pylori* uses the enzyme urease to convert urea to carbondioxide and ammonia in the stomach. Carbondioxide and ammonia having toxic effect for gastric mucosal epithelial cells and elevating acidic pH of the gastric lumen and impairing gastric epithelial functions such as mucus secretion. *H.pylori* is an important risk factor in development of peptic ulcer disease and chronic gastritis due to damage in the gastric mucosa[5].

H.pylori is effective in the etiology 95% of duodenal ulcer and 70–85% of stomach ulcer. Gastric cancer usually develops in atrophic gastritis and the risk of gastric cancer in patients with atrophic gastritis is 5–9 fold more than the normal population[56]. The issue that the individuals infected with *H.pylori* develop chronic gastritis is well known, the risk of atrophic gastritis and malignancies is not clear in these patients. However, *H.pylori* induced stomach ulcers and intestinal metaplasia[57].

H.pylori is also associated with metabolic syndrome, insulin resistance, diabetes and the development of diabetic complications as well as gastrointestinal disease[15]. The presence of *H.pylori* infection in patients with diabetes, glucose and lipid absorption is affected by gastrointestinal inflammation induced by *H.pylori* that may be a risk factor for ensuring blood glucose regulation in diabetic patients[58]. The presence of *H.pylori* infection in diabetic individuals is associated with microalbuminuria and albumin/creatinine ratio[59]. Additionally, inflammation which is caused by *H.pylori* is a risk factor for cardiovascular diseases[60]. Some mechanisms such as activation of proinflammatory and vasoactive components,

production of reactive oxygen species and changed ghrelin and leptin levels may explain the relationship between *H.pylori* and metabolic syndrome and insulin resistance[15]. *H.pylori* infection was significantly associated with metabolic syndrome, lower HDL, higher systolic blood pressure and higher LDL levels[60].

The relationship between *H.pylori* and obesity is complex. Obesity and metabolic syndrome are based on mostly genetic and lifestyle habits in individuals with *H.pylori* negative[2]. Some studies are suggested that the risk of *H.pylori* doesn't increase in obese individuals. Also, the presence of CagA antibodies and *H.pylori* bacteria have been shown not to be associated with BMI or serum leptin levels[61,62]. However, increase of appetite and BMI are associated with elevating plasma ghrelin levels after *H.pylori* eradication[47].

In the etiology of ischemic heart disease, the *H.pylori* is one of the frequently investigated issue. It can cause ischemic heart diseases by inducing the platelet activation and aggregation[63]. Also, the presence of folate deficiency is reported to be an another reason for the risk of ischemic stroke and myocardial cases seen in patients with *H.pylori* infection[64].

Neurological diseases are also thought to be associated with *H.pylori*. Neurological damage in Parkinson's patients is suggested to be associated with *H.pylori*[15]. Mitochondrial damage and autoimmunity caused by *H.pylori* is supposed to play a triggering factor for the mechanisms of Parkinson's disease[65]. There is a relationship between Alzheimer and *H.pylori* infection[66] and an improvement in cognitive and functional status in Alzheimer's disease patients in the case of *H.pylori* eradication was successful[67].

H.pylori infection plays a role in the pathogenesis of several skin diseases. In particular, the prevelance of *H.pylori* infection was reported to be high in patients with utricaria and it is associated with an increased risk of chronic urticaria[68]. Acne rosacea, which is associated with *H.pylori* and gastritis, is another skin disease. *H.pylori* is associated with the aetiology of rosacea, as a triggering factor and *H.pylori* eradication treatment provides symptomatic relief in patient with acne rosacea[64,69].

H.pylori infection is related with reduced growth rate in older children and exposure to *H.pylori* infection in early childhood causes malnutrition and growth retardation in particular in the presence of insufficient food intake[70]. *H.pylori* infection can lead to a series physiological changes that influence morbidity and mortality in childhood. Hypochlorhydria is associated with *H.pylori* infection in adults and children. Hypochlorhydria leads to malabsoption of several nutrients and increases susceptibility to enteric infections such as giardiasis, cholera, typhoid and nontyphoidal salmonellosis. These enfections lead to diarrhea which may lead to malnutrition and growth retardation in children[2].

Conclusion

H.pylori infection affects 50% of the world's population with the prevalence being the highest in developing countries[1]. *H.pylori* is associated with several diseases especially gastrointestinal system disease. In the presence of bacteria, results in malabsorption and malnutrition causing changes in appetite via affecting gastrointestinal hormone levels[12,15,19]. As a consequences of malabsorption, bioavalilability of some micronutrients decreases. In particular iron, vitamin B_{12} and folic acid deficiency seen in patients with *H.pylori* infection[2,43]. Certain foods and nutrients are effective for the prevention and the eradication therapy of *H.pylori*. In order to achieve the best results in preventing the disease, promoting healthy diets and lifestyle strategies must fully recognize the essential role of healthy nutrition throughout the entire life course.

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KAPSAM

Kafkas Tip Bilimleri Dergisi (KTBD) Türkçe ve İngilizce yazılmış makaleleri kabul eden, hakemli bir genel tıp dergisidir. Dergi tıbbi bilimleri geliştiren ve aydınlatan ya da okuyucularını eğiten orijinal sağlık ile ilgili makaleleri (araştırma, kısa bildiri, derleme, editöre mektup, olgu sunumu, çeviri, tıbbi yayın tanıtma vb türlerden yazılar) yayımlar. Yılda 3 sayı halinde (Nisan, Ağustos, Aralık) tek cilt olarak, matbu ve elektronik ortamlarda basılır. Dünyanın her yerinden makaleler kabul edilir.

MAKALE GÖNDERME

Makale toplama ve değerlendirme işlemleri http://meddergi.kafkas.edu.tr web adresinden online yapılır. Web adresinden giriş yapılmasını takiben "online makale gönder, takip et, değerlendir" butonunun tıklanması ile çıkacak direktiflerin takip edilmesi gereklidir. Online sistemde makale yüklenirken Başlık Sayfası, Makalenin tam metni, Telif Hakkı Devir Formu belgelerinin yüklenmesi zorunludur. Dergi, Uluslararası Tıp Dergileri Editörleri Komitesi'nin (ICMJE) rehberlerine sıkıca bağlıdır (http://www.icmje.org/index.html).

ETİK SORUMLULUKLAR

Dergi, Yayın Etikleri Komitesi'nin (COPE) rehberlerindeki iyi yayın uygulamaları ilkelerine sıkı bir şekilde bağlıdır (http://publicationethics.org/resources/guidelines). Makale başvurusunda bulunan yazarlar; çalışmalarının etik, hukuki ve bilimsel kurallara uygun olduğunu, daha önce yayınlanmamış ve başvuru sırasında başka bir yerde yayınlanmak için değerlendirme aşamasında olmadığını kabul ederler. Daha önce yayınlanmış tablo, şekil ve yazı makalede açıkça belirtilmeli ve yayın haklarını elinde tutanlardan izin alınmalıdır. Dergi, uygun etik kurul başvurularının yapılmış olmasını, bilgilendirilmiş onamların alınmasını ve bunların makalede bildirilmesini zorunlu tutar. İnsan öğesini içeren tıbbi çalışmalarda, Helsinki Deklarasyonu ilkelerine sıkıca bağlıdır (http://www.wma.net/e/policy/pdf/17c.pdf). Yazarlar, laboratuar hayvanlarının kullanımında ve bakımında kurumsal ya da ulusal rehberlere uygun davrandıklarını bildirmek zorundadır.

MAKALE HAZIRLANMASI

Makale Times New Romans yazı karakteri ile 12 punto ve 1.5 satır aralıklı olarak yazılmalıdır. Tüm makale boyunca ana başlık dahil tüm başlıkların kelimeleri büyük harfle başlayıp küçük harfle devam etmelidir. Makalenin bölüm başlıkları (**Giriş, Materyal** ve **Metot** gibi) altlarında kullanılan diğer başlıkların sadece ilk harfi büyük diğer tüm harfleri küçük harf olmalı ve bu başlıklar italik karakterde (örn. *Örneklemin seçimi*) yazılmalıdır. Makaleler açık, kısa ve akıcı bir Türkçe veya İngilizce ile yazılmalı, imla kurallarına uyulmalıdır. Dergi, özellikle giriş ve tartışma kısmı olmak üzere, makale uzunluğunu içerdikleri bilgiyle orantılı ölçüde kısa tutulmasını önerir. Bütün yazarlara bir istatistik uzmanı ile görüşmeleri önerilir.

Başlık Sayfası: Makale başlığı kısa ve devamlı nitelikte olmalıdır. Başlık indeksleme ve bilgi toplama açısından yararlı olacak biçimde tanımlayıcı ve bilgi verici olmalıdır. Bütün yazarların ad ve soyadları açık biçimde yan yana yazılmalıdır. Her yazar için çalıştığı bölüm, kurum ve şehir belirtilmelidir. İletişim yazarının şehir, ülke ve posta kodunu da içeren tam yazışma adresi, faks ve telefon numarası ile E-mail adresi sunulmalıdır. Burada sunulan yazar bilgileri makale yüklenirken kullanılan diğer hiçbir belgede bulunmamalıdır.

Özet: Özet anlaşılır olmalı ve yazının amaç ve belirgin sonuçlarını içermelidir. Yalnızca temel bulgu ve sonuçları belirterek, uyarlanmaya gerek duymadan özetleme servislerince kullanılabilmelidir. Araştırma makalelerinde özet bölümü şu alt baslıkları (**Amaç, Materyal ve Metot, Bulgular, Sonuç**) içermelidir. Derlemeler ve olgu sunumlarında alt başlıklar kullanılmaz. Editöre mektup gibi türlerde özetleme yapılmaz. Özet 300 kelimeden uzun olmamalı, yalnızca standart kısaltmalar kullanılmalıdır. Türkçe sunulan makalelerde ek olarak İngilizce özet, İngilizce sunulan makalelerde ek olarak Türkçe özet istenmektedir. Online sisteme yüklenen ana makale metninde başlığın altında her iki dildeki özet bölümü de bulunmalıdır.

Anahtar Kelimeler: Yazıyla ilgili "Index Medicus: Medical Subject Headings" standartlarına uygun en az 3 anahtar kelime özet altına yazılmalıdır.

Giriş: Anlaşılır ve kısa olmalı, son paragrafında çalışmanın amacı açıkça belirtilmelidir. Literatürün gözden geçirilmesi çalışmanın nedenselliğine yönelik olmalı ve önemli bilgileri içermelidir.

Materyal ve Metot: Gözlemsel ya da deneysel çalışmalarda katılımcılarının neye göre seçildiği (hastalar, kontroller ya da laboratuvar hayvanları) açıkça tanımlanmalıdır. Katılımcıların yaş, cinsiyet ve diğer önemli özellikleri belirlenmelidir. İnsan ve hayvanlar üzerinde yapılan çalışmalarda etik standartlar açıkça tanımlanmalı ve bu çalışmalar için önceden alınan etik kurul onay belgesinin alındığı yer, tarih ve sayı numarası verilmelidir. Yazarlar, diğer araştırmacılar tarafından da bulguların tekrarlanabilmesi için yöntem, cihaz (üreticinin adı ve menşei olan ülke parantez içinde verilmelidir) ve işlemleri yeterli açıklıkta tanımlamalıdırlar. İstatistiksel yöntemler de dahil, daha önceden kabul görmüş yöntemler için referanslar sağlanmalıdır. Yeni ya da uyarlanmış eski yöntemler tanımlanmalı, neden kullanıldıkları ve sınırları açıklanmalıdır. Bütün ilaç ve kimyasalların jenerik isimleri, dozları ve uygulanma yolları sunulmalıdır. Randomize kontrollü klinik çalışmalarda, çalışmanın ana öğeleriyle ilgili, çalışma protokolü (çalışma popülasyonu, müdahaleler ya da maruziyetler, beklenen sonuçlar ve istatistik analizin nedenselliği), müdahalelerin belirlenmesi (randomizasyon yöntemi, gruplara ayırmada gizlilik) ve grupların maskelenmesini (körleme) içeren özellikler sunulmalıdır. Bu bölümün son paragrafında mutlaka kullanılan istatistiksel analiz yöntemleri belirtilmelidir.

Bulgular: Tablo, şekil ve yazıda sunulan bilgilerin gereksiz tekrarlanmasından kaçınılmalıdır. Yalnızca tartışma ve ana sonucun anlaşılması için gerekli olan önemli bilgiler sunulmalıdır. Veriler bütünlük içinde ve tutarlı olarak sunulmalı, raporun açık ve mantıksal ilerlemesi sağlanmalıdır. Tablo ve şekillerdeki veriler yazıda tekrarlanmamalı, yalnızca önemli gözlemler vurgulanmalı ya da özetlenmelidir. Aynı veriler hem tablo hem de grafiklerde sunulmamalıdır. Verilerin yorumlanması tartışma bölümüne saklanmalıdır. Bu kısımda verilen istatistiksel sonuçların ve simgelerin genel makale yazım kurallarına uygun olması gerekmektedir.

Tartışma: Tartışma asıl bulguları anlatan kısa ve özlü bir cümle ile başlamalı, çalışmanın güçlü ve zayıf yönlerini tanımlamalı, bulguları diğer çalışmalarla ilişkilendirerek tartışmalı, olası açıklamalar sağlamalı ve gelecekte yanıtlanabilecek sorulara işaret etmelidir. Tartışma, bulgular bölümünde zaten sunulmuş bulguların tekrarıyla değil, bunların önceden bilinenlerle yorumlanması ile ilgilenmelidir. Sonuç bölümü tartışma kısmının son paragrafı olacak şekilde verilmelidir. Burada çalışmanın amacıyla ilişkilendirilebilir kısa önerilerde bulunulmalıdır ve niteliksiz önermelerden ve verilerle desteklenmeyen sonuçlardan kaçınılmalıdır.

Teşekkürler: Teşekkürler kısa ve net olmalı, yalnızca bilimsel/teknik destek ve finansal kaynak için yapılmalıdır. Rutin kurum olanaklarının kullanılması, makale hazırlanmasındaki destek ya da yardımlar (yazma işi ya da sekreterlik işleri) gibi durumları içermemelidir.

Kaynaklar: Literatüre atıfta bulunan kaynaklar ardışık olarak sıralanmalı ve makalenin sonunda yer almalıdır. Yazının bütününde atıflar üst karakterle cümle bitiminde noktadan önce yer almalıdır. Olabildiğince yazı içinde yazar isimleri kullanmaktan kaçınılmalıdır. Metinde yazar adı verildiğinde atıf numarası cümle sonunda değil, hemen yazarın adının sonrasında olmalıdır. Altı yazardan fazla yazarlı makalelerde altıncı yazardan sonra et al. ile kısaltma yapmak gerekir. Sayfa numaraları kısaltılarak yazılmalıdır (örn., 51-9).

Altı veya az yazarlı makale: Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med 2002; 347:284-7.

Altıdan fazla yazarlı makale: Pulgar VM, Yamaleyeva LM, Varagic J, McGee CM, Bader M, Dechend R, et al. Increased angiotensin ıı contraction of the uterine artery at early gestation in a transgenic model of hypertensive pregnancy ıs reduced by ınhibition of endocannabinoid hydrolysisnovelty and significance. Hypertension 2014; 64(3):619-25.

Kitap bölümü: Cooke DJ, Philip L. To treat or not to treat? An empirical perspective. In: Hollin, C.R. ed. Handbook of offender assessment and treatment. Chichester: Wiley, 2001:3-15.

Kitap: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002:93-113.

İnternet verisi: Cancer Research UK. Cancer statistics reports for the UK, http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/; 2003 [accessed 13.03.03].

Tablolar: Tablolar makale ana metninden ayrı, tek bir belge olarak Word belgesi şeklinde verilmelidir. Tüm tablolar tek bir belge içinde sunulmalıdır. Tablo başlıkları tablonun üstünde bulunmalı, sıra numarası içermeli ve başlığın ilk harfi dışındaki tüm harfleri küçük olmalıdır (örn., Tablo 1. Hastaların demografik özellikleri). Tablo içindeki kısaltmalar tablo altında açıklanmalı ve verilen rakamların birimleri unutulmamalıdır.

Şekiller: Tüm çizimler, fotoğraflar, radyolojik grafiler bu başlık altında toplanır. Şekiller makale ana metninden ayrı bir belge olarak verilmelidir. Tüm şekil başlıkları şeklin altında bulunmalı, sıra numarası içermeli ve başlığın ilk harfi dışındaki tüm harfleri küçük olmalıdır (örn., Şekil 1. Batının postoperatif direkt grafisi).

Grafikler: Grafikler makale ana metninden ayrı bir belge olarak verilmelidir. Tüm grafik başlıkları grafiğin altında bulunmalı, sıra numarası içermeli ve başlığın ilk harfi dışındaki tüm harfleri küçük olmalıdır.

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Articles with up to six authors: Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002; 347:284–7.

Articles with more than six authors: Pulgar VM, Yamaleyeva LM, Varagic J, McGee CM, Bader M, Dechend R, et al. Increased angiotensin ıı contraction of the uterine artery at early gestation in a transgenic model of hypertensive pregnancy ıs reduced by ınhibition of endocannabinoid hydrolysisnovelty and significance. Hypertension 2014; 64(3):619–25.

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