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The oncological outcome of the patients with ovarian clear cell cancer: Platinum-based adjuvant chemotherapy is not suitable

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Ethics Committee Approval
The study protocol was approved by Etlik Zubeyde Hanim Women's Health Training and Research Hospital institutional review board. (12.04.2019-07).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Ovarian clear cell cancer (OCCC) is one of the rare histological subtypes of epithelial ovarian cancer with different tumoral biology and prognosis. This study aimed to evaluate the clinical and pathological data of OCCC and define the prognostic factors.
Methods: Sixty-three patients with OCCC were included in this retrospective cross-sectional study. Patients with mixed-type clear cell carcinoma were excluded. Response to chemotherapy was assessed according to the WHO criteria. The survival analysis was performed using the Kaplan-Meier method and survival curves were compared with the log-rank test. Cox proportional hazards model was used in the multivariate analysis.
Results: The mean age of patients was 54.6 (10.7) years. Twenty-three (36.5%) patients were stage III&IV. Systematic lymphadenectomy was performed in 55 (87.3%) patients and 13 (23.6%) had lymph node metastasis. Maximal cytoreduction was performed in 57 (90.5%) patients, optimal cytoreduction, in 1 (1.6%) patient, and suboptimal cytoreduction was performed in 2 (3.2%) patients via primary cytoreductive surgery. The complete clinical response rate following adjuvant treatment was 61.1% in stages III&IV. Five-year failure-free survival was 63% in the entire cohort. According to the multivariate analysis, the stage was an independent risk factor for treatment failure. The probability of recurrence increased 24 times in stages III and IV (95% Confidence interval: 5.561-104.421; $P<0.001$).
Conclusion: The stage of the disease is a prognostic factor for OCCC. The response to platinum-based chemotherapy in OCCC is very low.

Keywords: Ovarian clear cell cancer, Recurrence, Stage, Survival

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Introduction

Epithelial ovarian cancer (EOC) is the second most common gynecological cancer in developed countries and the most common cause of death due to gynecological malignancies [1]. Ovarian clear cell cancer (OCCC) is one of the rare histological subtypes of epithelial ovarian cancer with different tumoral biology and prognosis [2]. Approximately 30% of EOC patients in East Asia and 10% in Europe and America were diagnosed with OCCC [3]. In addition to diagnosis at an early stage and young age, it is often associated with endometriosis [4].

The treatment of OCCC is the same as the other EOC subtypes. Staging surgery is recommended, including total hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-paraaortic lymphadenectomy, and omentectomy. The purpose of surgical treatment, especially in advanced-stage disease, should be to perform the surgery without leaving any residual tumor [5].

The classical combination of platinum and taxane used in EOC is considered the standard adjuvant therapy for OCCC [6]. However, it has a relatively poor prognosis and increased chemoresistance compared with other EOC subtypes. The 5-year overall survival decreases to 85-90% in stage 1 cases, and 15-20% in stage 4 cases despite conventional treatments [7, 8]. The survival data of OCCC are better than that in high-grade serous ovarian cancer at the early stages and poorer at advanced stages [7]. This might be caused by the partial response to conventional adjuvant therapy [6].

Developing optimal treatment strategies is complicated due to the rarity of OCCC, insufficient data, and increased resistance to chemotherapy compared to the other subtypes. This study aimed to evaluate the clinicopathological data and survival rates of patients with OCCC and identify prognostic factors that determine survival and recurrence.

Materials and methods

A total of 1381 patients with EOC who were treated in the gynecological oncology clinic between 1990-2019 were retrospectively enrolled in this study. Eighty patients were diagnosed with OCCC as a subtype of EOC. Patients with synchronized tumors, secondary malignancies, a tumor with non-epithelial and non-clear cell components, who have received neoadjuvant therapy, who were operated on elsewhere, and those with insufficient data were excluded. A study group was formed with a total of 63 patients.

Demographic characteristics, intraoperative findings, postoperative pathological characteristics, types of adjuvant therapy received, and oncological outcomes of patients were retrieved from the hospital database. The study protocol was approved by Etlik Zubeyde Hanim Women's Health Training and Research Hospital institutional review board (12.04.2019-07).

In our clinic, the routine staging surgery in ovarian cancers includes exploration of the abdomen, peritoneal cytological sampling, total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, and systematic retroperitoneal lymphadenectomy. In the presence of a macroscopic tumor, maximal cytoreduction is aimed with cytoreductive surgery techniques in addition to staging surgery. Maximal cytoreduction is defined as no visible tumor, optimal cytoreduction is defined as a residual tumor with ≤1 cm diameter, and suboptimal cytoreduction is defined as >1 cm residual tumor at the end of the surgery. All surgical procedures were performed by experienced gynecological oncology surgeons. Adjuvant treatment options were decided by the gynecologic oncology tumor council.

Patients who had a complete clinical response after completion of the initial treatment were followed up quarterly for the first 2 years, semi-annually up to 5 years, and then annually thereafter with a pelvic examination, abdominal-pelvic ultrasound, complete blood count, blood chemistry, and tumor markers. Chest X-ray screening was performed once a year and if necessary, thoracic and/or abdominal computed tomography was performed.

We defined recurrence distal to the pelvic inlet as pelvic recurrence, between the pelvic inlet and diaphragm as abdominal recurrence, and the remaining types of recurrences as extra-abdominal recurrence. Recurrence in the liver parenchyma, skin, and bone was considered an extra-abdominal recurrence.

The 2014 International Federation of Gynecology and Obstetrics (FIGO) staging criteria were used. For patients treated before 2014, cancer staging was modified according to the FIGO 2014 system using surgical and pathological evaluation. Response to chemotherapy was assessed per the WHO criteria [9]. The response to chemotherapy in patients with measurable lesions was evaluated using clinical, biochemical (CA-125), and imaging (CT or magnetic resonance) parameters one month after the end of adjuvant chemotherapy. Complete clinical response (1) was defined as no visible macroscopic tumor, and partial clinical response (2) was defined as a >50% decrease in macroscopic tumor size. Stable disease (3) was defined as a <50% decrease or <25% increase in macroscopic tumor size and progressive disease (4) as the detection of a new lesion and/or a >25% increase in macroscopic tumor size.

Disease progression during initial adjuvant chemotherapy was defined as a refractory disease. The same adjuvant chemotherapy protocol was administered to the patients with partial clinical response and stable disease. During the adjuvant chemotherapy process, patients were re-evaluated and, finally, they were classified as having complete clinical response or refractory disease. Radiological (detection of new lesions) and laboratory evidence of (increase in CA-125 levels) recurrence in patients with complete clinical response was considered a recurrent disease. Both refractory disease and recurrent disease were defined as disease failure.

The time from the first surgery to death because of the disease or last follow-up visit was defined as overall survival (OS). Failure-free survival (FFS) was defined as the period from initial surgery to proven recurrence or refractory disease with clinical examination and/or radiological imaging or the period from initial surgery to the last follow-up visit in those who did not develop refractory/recurrent disease.

Statistical analysis

SPSS 20.0 (SPSS Inc., Chicago, IL) was used for data review and statistical analysis. Descriptive statistics were expressed as mean (standard deviation) and median (min-max)

for continuous variables and n (%) for categorical variables. The Kaplan-Meier method was used to evaluate survival results. Survival curves were compared in the log-rank test. All variables with a *P*-value of <0.05 in the univariate analysis, except those associated with the stage, were included in the multivariate analysis. Multivariate analysis was conducted by use of the Cox proportional hazards model to assess independent factors affecting survival. All *P*-values less than 0.05 were considered statistically significant.

Results

The mean age of 63 patients included in the study was 54.6 (10.7) years (range: 18-86 years). The median preoperative CA-125 value was 163 IU/ml (range: 5-2165 IU/ml). According to the FIGO 2014 criteria, 37 (58.7%) patients were stages I and II, and 23 (36.5%) were stages III and IV. The data of three patients were inadequate for determining the stage. Ascites was detected in 11 (17.5%) patients and the median ascites volume was 500 ml (range: 100-8500 ml). Systematic lymphadenectomy was performed in 55 (88.3%) patients. The median number of lymph nodes removed in those who underwent lymphadenectomy was 59 (range: 11-112), a median of 41 (range: 1-76) were removed from the pelvic region, and 24 (range: 8-46), from the paraaortic region. Thirteen (23.6%; n=13/55) had lymph node metastasis and the median metastatic lymph node number was 6 (range: 1-14). The tumor was bilateral in 13 (20.6%) patients. Positive peritoneal cytology was present in 17 (27%) patients and omental metastasis was seen in 14 (22.2%). Endometriosis was present in 11 (17.5%) patients. Maximal cytoreduction was achieved in 57 (90.5%) patients, optimal cytoreduction was achieved in 1 patient, and 2 (3.2%) patients were suboptimally cytoreduced. Cytoreduction data of three patients could not be obtained. Detailed clinical, surgical, and pathological characteristics of patients are presented in Table 1.

Table 1: Patients' characteristics

Characteristics			Mean(SD)	Median (range)
Age			54.6(12.29)	54 (18-86)
Ca 125 (IU/ml)			319.2(436.25)	163 (5-2165)
Ca 19-9 (IU/ml)			136.8(116.24)	180 (2-263)
Ascites volume (cc)			2054.6(2976.70)	500 (100-8500)
Number of removed lymph node			59.6(20.07)	59 (11-112)
Number of removed pelvic lymph node			38.2(19.47)	41 (1-76)
Number of removed paraaortic lymph node			24.3(10.06)	24 (8-46)
Number of metastatic lymph node			6.38(3.50)	6 (1-14)
			n	%
FIGO 2014 stage	Stages I-II		37	58.7
	Stages III-IV		23	36.5
	Not determined		3	4.8
Outcome of cytoreductive surgery	Suboptimal (residue tumor > 1cm)		2	3.2
	Optimal (residue tumor ≤ 1cm)		1	1.6
	Maximal (no residue tumor)		57	90.5
	Not determined		4	6.3
Ascites	Present		11	17.5
	Absent		50	79.4
	Not reported		2	3.2
Peritoneal Cytology	Positive		17	27
	Negative		29	46
	Not reported		17	27
Ovarian tumor laterality	Bilateral		13	20.6
	Unilateral	Left	22	34.6
		Right	22	34.6
	Not reported		6	9.5
Omental involvement	Present		14	22.2
	Absent		48	76.2
	Not reported		1	1.6
Peritoneal involvement	Present		8	12.7
	Absent		54	85.7
	Not reported		1	1.6
Endometriosis	Present		11	17.5
	Absent		45	71.4
	Not reported		7	11.1
Lymphadenectomy	Performed		55	87.3
	Not performed		5	7.9
	Not reported		3	4.8
Lymph node metastases [1]	Present		13	23.6
	Absent		41	74.6
	Not reported		1	1.8
Site of metastatic lymph node	Only pelvic		3	4.8
	Only paraaortic		5	7.9
	Pelvic and paraaortic		5	7.9

SD: Standard deviation, [1]: Lymph node metastasis was evaluated in 55 patients who underwent lymphadenectomy

Adjuvant chemotherapy and survival analysis

Due to insufficient data or patients lost to follow-up during the postoperative treatment process, 8 patients were excluded, and survival analysis was performed with a total of 55 patients. Fifty-three (96.4%) patients received chemotherapy, while two patients refused. These two patients were stage IA according to the FIGO 2014 criteria and recurrence did not occur during 41 and 133 months of follow-up. All patients received platinum-based chemotherapy (Table 2).

Progression was detected in 7 (12.7%) patients during adjuvant chemotherapy, which was defined as a refractory disease. All these patients were stages III & IV. Complete clinical response to adjuvant chemotherapy was achieved in 11 (61.1%) of 18 patients with stages III and IV; however, refractory disease was detected in 7 (38.9%).

Following adjuvant chemotherapy, recurrence occurred in 11 (20%) of 48 (87.3%) patients with complete clinical response. The median time to recurrence in this group was 14 months (range: 6-48 months).

Table 2: Adjuvant chemotherapy and disease failure pattern

Characteristics		Mean (SD)	Median (range)
Follow-up (months)		58.7 (56.50)	42 (3-260)
Time to recurrence (month) [1]		19.9 (14.27)	14 (6-48)
		n	%
Adjuvant therapy	Not received	2	3.6
	Received	53	96.4
Type of adjuvant chemotherapy	Cyclophosphamide + Epirubicin+ Cisplatin	1	1.8
	Paclitaxel + Carboplatin	44	80
	Paclitaxel + Cisplatin	7	12.7
	Paclitaxel + Carboplatin + Epirubicin	1	1.8
Response to adjuvant chemotherapy [1]	Complete clinical response	48	87.3
	Progressive disease	7	12.7
Recurrence [1,2]	Negative	37	67.3
	Positive	11	20
Disease failure [1]	Negative	37	67.3
	Positive	18	32.7
Disease failure pattern	Only abdominal	13	23.6
	Only pelvic	1	1.8
	Abdominal and pelvic	1	1.8
	Thoracic	1	1.8
	Thoracic and abdominal	1	1.8
	Thoracic and pelvic	1	1.8

SD: Standard deviation, Disease failure: Progressive disease and recurrence, [1]: Survival analysis was done with 55 patients, [2]: Recurrence in patient with complete clinical response.

Eighteen (32.7%) patients had "disease failure" (Figure 1). The cancer was in the abdomen in 13 (23.6%), in the pelvic region in 1 (1.8%), in the pelvic and abdominal regions in 1 (1.8%), in the thorax 1 (1.8%), in the thorax and abdomen in 1 (1.8%), and in the thorax and pelvis in 1 (1.8%). Detailed information about adjuvant therapy and disease failure is shown in Table 2.

Figure 1: Cohort chart

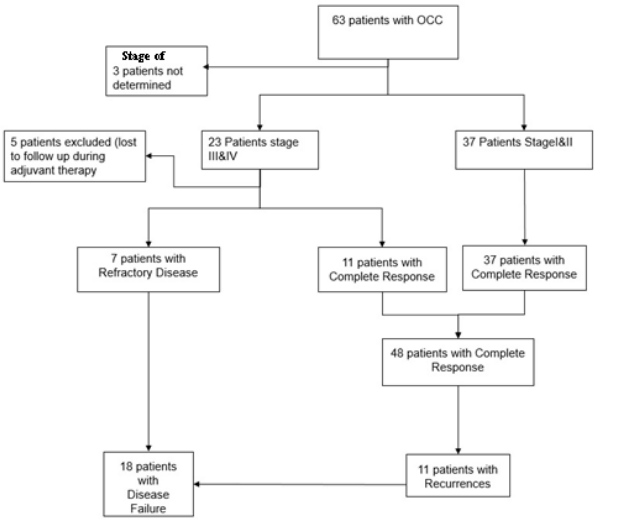
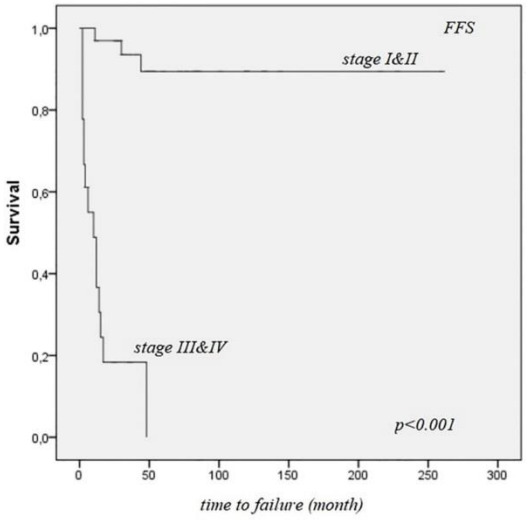


Figure 2: Relationship between failure-free survival and stage Kaplan-Meier Analysis



The median follow-up period of 55 patients who underwent survival analysis was 42 months (range: 3-260 months). Only 2 patients died because of the disease during the follow-up period. Therefore, statistical analysis could not be performed to identify the prognostic factors affecting OS. The 5-year FFS rate was 63%. In univariate analysis, advanced stage, the presence of ascites, lymph node metastases, bilateral ovarian tumors, peritoneal involvement, omental metastasis, rupture of the capsule, surface involvement, and positive peritoneal cytology were unfavorable prognostic factors for FFS (Table 3).

Lymph node metastasis, positive peritoneal cytology, peritoneal spread, and omental metastasis are highly correlated with stage; therefore, a multivariate analysis model was created with the stage (III&IV *vs.* I&II), ascites (present vs. absent), site of ovarian tumor (bilateral vs. unilateral), capsule rupture (positive vs. negative), surface involvement (positive vs. negative) (Table 3). Only stage was an independent risk factor for disease failure (Hazard Ratio; 24.1, 95% Confidence interval: 5.561-104.421; $P<0.001$). In stages I and II, the 5-year-FFS was 89%, and in stages III & IV, it was 0% ($P<0.001$) (Figure 2).

Table 3: Factors predicting failure-free survival

Factors		Univariate Analysis 5-year Failure-Free Survival		Multivariate Analysis Risk of Disease Failure		
		Percentage	*P*-value	Hazard Ratio	95% Confidence Interval	*P*-value
Age [1]	≤54 years	59	0.325			
	>54 years	73				
FIGO 2014 stage	I&II	89	<0.001	1 (ref.)	5.561-104.421	<0.001
	III&IV	0		24.1		
Preoperative CA 125 level (IU/ml)	≤35	83	0.172			
	>35	55				
Ascites	Absent	74	0.001	1 (ref.)	0.552-5.192	0.357
	Present	20		1.693		
Lymph node metastasis	Negative	77	<0.001			
	Positive	20				
Number of removed lymph node [1]	≤59	50	0.072			
	>59	71				
Site of ovarian tumor	Unilateral	79	<0.001	1 (ref.)	0.712-8.738	0.153
	Bilateral	0		2.496		
Peritoneal involvement	Negative	72	0.002			
	Positive	0				
Omental metastasis	Negative	79	<0.001			
	Positive	0				
Capsule rupture	Negative	66	0.004	1 (ref.)	0.409-3.852	0.690
	Positive	27		1.256		
Capsule surface involvement	Negative	77	0.003	1 (ref.)	0.490-5.299	0.387
	Positive	38		1.758		
Peritoneal cytology	Negative	91	<0.001			
	Positive	8				
Endometriosis	Negative	58	0.087			
	Positive	91				

[1]: Median value, ref: reference

Discussion

Ninety percent of ovarian tumors have an epithelial origin. EOC is a heterogeneous group with eight histological subtypes according to the World Health Organization (WHO) classification [10]. Treatment strategies of all histological subtypes are currently similar, and whether adjuvant chemotherapy will be administered is determined by tumor stage and grade rather than tumor subtype. However, each EOC subtype has different clinical and molecular features, and their oncological outcomes are disparate [11]. Liu et al. [7] reported the 5-year disease-specific survival rate in epithelial ovarian cancer as 66.4% in clear cell subtype, 71.4% in mucinous subtype, 80.3% in endometrioid subtype, and 42.4% in the serous subtype. However, in the current study, the oncological outcome of the patients with advanced-stage OCCC was poorer than those with serous and endometrioid type ovarian cancers.

Maximal cytoreduction was achieved in 90.5% of the patients and 96.4% received adjuvant chemotherapy. The univariate analysis revealed that the stage of the disease, presence of ascites, lymph node metastasis, peritoneal involvement, omental metastasis, capsule rupture, surface involvement, and positive peritoneal cytology were significant for disease failure. These results are in line with previous findings in the literature investigating prognostic factors in OCCC [12-15].

In multivariate analysis, the stage was an independent prognostic factor for disease failure in OCCC, and the risk of disease failure increased 24 times in the advanced stage. Five-year FFS rates were 89% in stages I&II and 0% in stages III& IV. Studies show that the prognosis is better in the early stages of OCCC [7, 13-15]. In a study reported by Lee et al, the 3-year relapse-free survival rates were 80%, 47%, 34%, and 30% at stages I, II, III, and IV, respectively [13].

The current treatment strategy for OCCC is aggressive surgery and platinum-based adjuvant chemotherapy. However, poor prognosis is often observed in patients with advanced-stage, which is considered to be mostly due to the resistance to conventional platinum-based chemotherapy [16]. The clinical response rate to platinum-based chemotherapy in the EOC group was 70-80% in high-grade serous ovarian cancer, 26.3% in advanced mucinous ovarian cancer, 23.1% in low-grade serous

ovarian cancer, and 20-55% in the OCCC group [17-21]. Opposite to other EOC types of OCCC, partial resistance to platinum-based chemotherapy and the absence of adequate alternative therapies other than platinum-based combinations complicate the treatment of the disease.

Zhao et al. reported the chemosensitivity rates in the OCCC group as 91.4% at stages I and II and 36.7% at stages III and IV [14]. Thang et al. achieved maximal cytoreduction in 90% of patients in their study including 130 OCCC patients. They administered adjuvant platinum-based chemotherapy to all followed-up patients (n=127), the rate of chemotherapy-refractory or resistant disease was 23% in the entire cohort and 64.5% in stage III-IV cases. They found that stage and chemotherapy resistance were independent prognostic factors in survival analysis [15].

OCCCs are considered high-risk EOCs because they behave more aggressively. Adjuvant chemotherapy is recommended, even with stage IA [22]. However, with the current information about chemotherapy resistance in OCCC, the benefit of this approach is controversial. Oseledchyk et al. evaluated a total of 1995 stage I OCCC patients and stated that platinum-based adjuvant chemotherapy did not improve OS [23]. In their study using SEER data, Bogani et al. [20] reported that chemotherapy was not beneficial at stages IA-B in OCCC although it improved overall survival data at stage IC.

Considering the high maximal cytoreduction and adjuvant treatment rates in our study, the high rate of disease failure (32.7%) and the progression of the disease observed in about %40 of patients in the advanced stages despite chemotherapy indicates both the aggressive behavior and non-responsiveness to chemotherapy of the OCCC.

Various results show that platinum-based chemotherapy may not be the most convenient treatment option for patients with OCCC. This led researchers to define alternative treatment combinations. However, NCCN (The National Comprehensive Cancer Network) guidelines still recommend the use of platinum-based chemotherapy in the treatment of OCCC [22]. In their randomized phase III study comparing the irinotecan + cisplatin combination with the paclitaxel + carboplatin combination in OCCC management, Sugiyama et al. were unable to detect survival advantage in the irinotecan + cisplatin group [24]. In addition, in the treatment of OCCC, new molecular targets such as epidermal growth factor receptor (EGFR), phosphatidylinositol 3'-kinase (PI3K) signaling pathway and, mitogen-activated protein kinase (MAPK) were identified and tested with no consensus on their effectiveness [25-27].

Considering the aggressiveness of OCCC, low response rates to first-line platinum-based adjuvant chemotherapy, and the fact that an effective chemotherapy regimen has not yet been found, it is clear that the most important step in the management of the disease is currently maximal surgical cytoreduction. Takona et al. [28] reported the median progression-free survival time in the OCCC group as 39 months in patients without residual tumor, 7 months in patients with residual tumors with <1 cm diameter, and 5 months in patients with residual tumors >1 cm in diameter. Patients without residual tumors had significantly better progression-free survival than those with a tumor smaller than 1 cm or a tumor diameter greater than 1 cm, whereas there was no significant prognostic difference between patients with a tumor diameter less than and greater than 1 cm. As reported above, this comparison could not be made due to the low rates of optimal and suboptimal cytoreduction. However, several studies state that residual tumor load in OCCC is an independent prognostic factor [13, 27, 28].

OCCC is generally diagnosed at a young age, frequently associated with endometriosis, detected in the early stages, and bilateral ovarian involvement is rare [4, 6, 7, 10, 29]. Our results are consistent with the previous findings. Studies detected endometriosis in 9-70% in OCCC patients [13, 30]. In our study, this rate was 17.5%.

The limitations of our study include the retrospective design and the small sample size. We demonstrated detailed clinical-pathological characteristics and adjuvant treatments of the patients. Most patients underwent complete staging and cytoreductive surgery, including systematic lymphadenectomy. Follow-up periods of the patients were long, and histopathological examinations were performed by experienced gynecological pathologists, all of which are the strengths of our study.

Conclusion

OCCC is a subtype of EOC with aggressive behavior, of which prognosis is determined by the stage of the disease. It partially responds to platinum-based adjuvant chemotherapy. Because effective adjuvant therapy has not yet been identified, the main goal in current OCCC management should be the absence of postoperative residual disease. Future studies on the current topic are therefore needed to better illuminate the molecular and genetic basis of OCCC and to define effective new chemotherapy combinations.

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Comparison of serum procalcitonin and interleukin-6 levels with CRP levels in the follow-up of antimicrobial treatment of patients with pyogenic and granulomatous vertebral osteomyelitis

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Ethics Committee Approval
This study was approved by Dumlupınar University Clinical Research Ethics Committee (date: July 21, 2016, No:2016-9/20).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Infection of the intervertebral disc and adjacent vertebrae is called vertebral osteomyelitis (VO). This study aims to determine whether procalcitonin (PCT) and interleukin (IL)-6 markers are more valuable than white blood cells (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the follow-up in patients with VO who were administered antibiotherapy.
Methods: All adult patients with a diagnosis of VO were included in this prospective cohort study. The patients were divided into two groups as those with pyogenic and granulomatous VO. Serum WBC, CRP, ESH, PCT and IL-6 levels were measured at baseline, and the 2nd, 4th, 8th and 12th weeks of antibiotherapy. The changes in the laboratory parameters of the patients during follow-up were evaluated.
Results: Of the 30 patients included in the study, there were 22 and 8 patients in the PVO and GVO groups, respectively. Baseline IL-6 measurement was above the reference in all patients, CRP was elevated in 96.6%, and PCT was increased in only one patient. Although there was a paradoxical increase in PCT values in the PVO group in the 2nd week compared to the pre-treatment values, a rapid decrease was observed in the 4th and 8th weeks. In the GVO group, the gradual decrease in PCT in parallel with the treatment response was considered to predict clinical improvement. IL-6 values decreased by 43.2% and 50% compared to baseline at the 4th and 8th weeks of treatment, respectively, in the PVO group. In the GVO group, a 50% reduction was detected in the 4th week of treatment compared to baseline.
Conclusion: PCT and IL-6 biomarkers are valuable indicators in treatment follow-up. Although not statistically significant, the most stable decrease was observed in IL-6. Using IL-6 for the follow-up of the patients with VO may prevent long-term antibiotherapy.

Keywords: Vertebral osteomyelitis, Interleukin-6, Procalcitonin, C-reactive protein

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Introduction

Infection of the intervertebral disc and adjacent vertebrae is called spondylodiscitis (SPD), disc space infection or vertebral osteomyelitis (VO) [1]. VO mostly develops iatrogenically. While spontaneous pyogenic VO (PVO) is rare [2], it is the most common form of hematogenous osteomyelitis over 50 years of age. It makes up for 3-5% of all osteomyelitis cases. In a study conducted in France, the incidence of spontaneous VO was 2.4 per 100.000 [3,4]. Iatrogenic VO may develop secondary to lumbar puncture, epidural injection, spinal surgery, and penetrating trauma [1, 5]. Postoperatively, the risk of developing VO ranges from 1-8% [6].

Etiologically, it can be divided into pyogenic and granulomatous VO. Brucellosis and tuberculosis (TB) are the most common granulomatous agents. Granulomatous VO (GVO) cases can also be seen due to actinomycosis, nocardiosis, syphilis and fungi [7]. Since TB is a treatable disease, PVO is more common [1, 3].

The diagnosis of VO is challenging. The disease is typically characterized by back pain unresponsive to conservative treatment, and elevation in serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Fever may not always be seen. Magnetic resonance imaging (MRI) is often used in diagnosis. Empirical treatment is not recommended in patients without sepsis or neurologic deficit until a microbiological diagnosis is made. Microbiological and pathological examination of tissue biopsy is important in diagnosis and treatment planning [3].

Procalcitonin (PCT) is a better parameter than ESR, CRP and white blood cells (WBC) in the diagnosis of bacterial infections [8]. The serum PCT increases more rapidly than CRP [9]. The plasma level of interleukin (IL)-6 rises rapidly within 1-3 hours in bacterial infections and acute inflammation; but it decreases within a short time [10]. Thus, it has the potential to show inflammation before the onset of clinical findings [11]. In the diagnosis of infection, IL-6 has lower sensitivity and higher specificity than CRP [12].

In the evaluation of treatment response, ESR and CRP follow-up is recommended with an assessment of clinical findings. ESR and CRP values may increase despite clinical improvement in some patients. The decrease trend in these biomarkers lowers the risk of treatment failure. However, in most patients, no significant decrease is observed in these biomarkers in 4-8 weeks of follow-up due to low specificity. Therefore, whether the values are compatible with clinical findings should be assessed [3]. These parameters can be easily affected by other infectious or non-infectious conditions [10, 13], which leads to confusing results in treatment management. The clinician may resort to unnecessary antibiotic revision, prolongation of the duration of antibiotic therapy, and unnecessary surgery. To the best of our knowledge, no study evaluates IL-6 and PCT in the treatment follow-up of patients with vertebral osteomyelitis in the literature. Our study aimed to examine whether the use of procalcitonin (PCT) and Interleukin (IL) 6, which are more specific for bacterial infections compared to ESR and CRP, in the follow-up of the treatment response of VO patients is more beneficial. Although monitoring the clinical response with PCT and IL-6 is more costly than assessing CRP, the use of these biomarkers will be cost-effective if they are shown to be more beneficial in clinical follow-up, reducing unnecessary antibiotic use, shortening the treatment duration, preventing unnecessary surgery, shortening hospitalization, reducing antibiotic-related side effects and surgery-related complications.

Materials and methods

Study design and sampling

This prospective study was conducted between August 2016 and January 2018. All adult patients visiting Afyon Kocatepe University, Department of Infectious Diseases and Clinical Microbiology who were diagnosed with VO were included in the study. Serum WBC, CRP, ESR, PCT and IL-6 levels were measured at baseline, and in the 2^{nd}, 4^{th}, 8^{th}, 12^{th} and 24^{th} weeks of antibiotherapy. The patients were divided into two groups as those with PVO and GVO. Inter- and intragroup analyses were conducted in terms of laboratory parameters during treatment follow-up. For each laboratory parameter, pre-treatment values within the same group were first compared with the mean values at each follow-up week. Then, the mean values in the follow-up weeks after the beginning of treatment were compared. Finally, the mean values between the two groups were compared at the same follow-up weeks.

Diagnostic criteria for VO were defined as follows:

- Presence of clinical findings consistent with the disease (spine pain with or without fever unresponsive to conservative symptomatic treatment, presence of neurological symptoms),
- Increased CRP and ESR values,
- Presence of spondylitis, discitis or SPD demonstrated by MRI/CT in the patient.

Exclusion criteria for the study were as follows:

- Younger than 18 years of age,
-VO associated with a non-infectious inflammatory condition (such as spondyloarthropathies)
- Presence of another concomitant focus of infection
- Not attending follow-ups regularly, missing laboratory tests

Peripheral blood cultures were obtained from all patients. Brucella tube agglutination test was used for brucellosis. Purified Protein Derivative (PPD) was performed for TB. Tissue biopsy was performed in patients who had no contraindications and accepted the operation. Biopsy analyses included Gram and Ehrlich-Ziehl-Neelsen (EZN) staining, aerobic, anaerobic culture, and Mycobacteria cultures.

Diagnosis of brucellosis VO was made if *Brucella spp*. were grown in cultures, or serum brucella tube agglutination titer was ≥1/160 or increased fourfold after two weeks. TB was diagnosed in cases where acid-fast bacilli (ARB) were detected by EZN staining, or *M. tuberculosis* was grown and/or chronic granulomatous inflammation was detected in tissue biopsy. In cases where no diagnostic intervention could be performed, patients with clinical symptoms, imaging, and laboratory findings suggestive of TB, those with a history of TB and positive PPD, or patients whose peripheral smear findings were compatible with TB were considered to have TB VO. The cases

that responded to the empirical antibiotic treatment, although pyogenic bacteria were grown in cultures were considered as PVO.

Serum CRP concentrations were measured by the nephelometric method (Beckman-Coulter, USA) and serum ESR levels were determined with Vacuplus ESR-120 brand sedimentation measuring device (LEN-MED Medical Health Services, Ankara, Turkey). Serum WBC measurements were made with Mindray BC-6800 brand hemogram device (Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China). IL-6 was measured with the DiaSource brand Human IL-6 ELISA kit (DIAsource Immunoassays S.A., Louvain-la-Neuve, Belgium). Absorbance reading was performed on a ChemWell 2910 brand ELISA reader device (Awareness Technology, Inc. Martin Hwy. Palm City, USA). Serum PCT was measured with Cloud-Clone brand Human PCT ELISA kit (Cloud-Clone Corp. Katy, USA). Absorbance reading was performed on a ChemWell 2910 brand ELISA reader device (Awareness Technology, Inc. Martin Hwy. Palm City, USA). Threshold values for WBC, CRP, ESR, PCT and IL-6 were $4x10^3$/uL, 0.8 mg/dL, 15 mm/h, 200 pg/mL, and 3 pg/mL, respectively [14-17].

Appropriate antibiotherapy was initiated according to the results of cultures in patients without sepsis or neurological deficits. Initial treatment of PVO included intravenous (IV) administration of antibiotics. Empirical antibiotherapy were given to cover possible pyogenic agents, such as staphylococci, streptococci and gram-negative bacilli (GNB). Empirical treatment comprised glycopeptide or daptomycin effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and quinolone, 3rd generation cephalosporin or carbapenem effective against GNB. Antibiotherapy was revised according to the results of microbiological sampling. Treatment was continued or revised according to the clinical and laboratory response in patients from whom no microorganisms were isolated. Patients who had a partial clinical response to the parenteral treatment were discharged with oral therapy after 2 weeks. After discharge, all patients were followed up with 2-week intervals while using antibiotherapy. At each control visit, the symptoms of the patients were questioned and serum WBC, CRP, ESR, PCT and IL-6 levels were measured.

The duration of treatment ranged between 8-24 weeks for PVO, and it was 24 weeks for patients with brucellar VO. In TB VO cases, the minimum duration of treatment was 24 weeks. Decrease in CRP and ESR values compared to baseline and complete regression of back pain were considered treatment response in patients.

Ethics statement

The study was approved by Dumlupınar University Clinical Research Ethics Committee (date: July 21, 2016, No:2016-9/20). All individuals included in the study were informed about the purpose and method of the study, and all signed the informed consent form.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 22 (Inc. Chicago, Illinois, USA) statistical package program. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Number of patients and frequency tables were used for categorical variables. Descriptive statistical data for normally distributed variables were expressed as mean ± standard deviation (SD). Non-normally distributed numerical variables were presented as median (minimum-maximum). The student t test was used to compare the means between two normally distributed independent groups, while the Mann Whitney-U test was used for non-normally distributed variables. Chi-square test was used to compare categorical variables. Repeated measures ANOVA test was utilized to compare the means between dependent groups. $P<0.05$ was considered statistically significant in all analyses.

Results

Among forty patients, eight were lost to follow-up, and two patients died. Therefore, the results of 30 patients were included in the study. Twenty-two (73.3%) had PVO while 8 (26.7%) had GVO. Among GVO cases, 6 (20%) had brucellosis and 2 (6.7%) had TB.

Fifteen (50%) of the patients included in the study were male and the mean age of all patients was 56.2 (16.0) years. Twenty-eight (93.3%) had spinal pain, 18 (60%) had fever, 17 (56.7%) had neurological deficit, 2 (6.7%) had hip pain, 1 (3.3%) had palpable swelling in the lumbar region, and 1 (3.3%) had palpable swelling in the groin. The mean time between the onset of symptoms and diagnosis was 11.6 (11.7) weeks. There was no significant difference between the groups in terms of gender, mean age, frequency of pain, fever and neurological deficit symptoms, and mean time until diagnosis.

In terms of risk factors, 13 (43.3%) patients had undergone spinal surgery, 6 (20%) had diabetes mellitus, 1 (3.3%) had received immunosuppressive therapy, 1 (3.3%) had a malignancy, and 1 (3.3%) patient had chronic liver disease. All patients with VO which developed after spinal surgery were in the PVO group. The mean time between VO onset and surgery was 16.6 (16.3) weeks. Demographic and clinical characteristics of the patients are shown in Table 1.

Table 1: Demographic and clinical characteristics of VO cases

	Pyogenic VO (n=22) Value (%)	Granulomatous VO (n=8) Value (%)	*P*-value	Total VO (n=30) Value (%)
Mean age (SD)	56.8 (14.3)	54.7 (21.2)	0.762	56.2 (16.0)
Gender (female/male)	11/11	4/4	1.000	15/15
Risk factors				
-History of spinal surgery	13 (59.1)	-	0.004	13 (43.3)
- Presence of comorbidity	13 (59.1)	5 (62.5)	0.866	18 (60)
*DM	4 (18.1)	2 (25)		6 (20)
*Malignancy	1 (4.5)			1 (3.3)
*Immunosuppressive therapy	1 (4.5)	-		1 (3.3)
*Chronic liver disease	1 (4.5)	-		1 (3.3)
Time from symptom to diagnosis (mean, weeks)	11.6 (11.7)	5.8 (4.4)	0.219	10.1 (10.5)
Symptoms				
Spinal pain	20 (90.9)	8 (100)	0.377	28 (93.3)
Fever	12 (54.5)	6 (75)	0.419	18 (60)
Neurological deficit	14 (63.6)	3 (37.5)	0.242	17 (56.7)
Hip pain	-	2 (25)		2 (6.7)
Swelling in the groin	1 (4.5)	-		1 (3.3)
Swelling in the waist	1 (4.5)	-		1 (3.3)

DM: Diabetes mellitus, VO: Vertebral osteomyelitis

MRI was performed in all patients. Eight (26.6%) patients were additionally scanned with CT. There was lumbar involvement in 19 (63.3%) patients, lumbosacral involvement in

6 (20%), thoracic involvement in 4 (13.3%), and cervical vertebral involvement in 1 (3.3%). There were abscesses in 13 patients (43.3%). Paraspinal abscess was observed in 6 (20%), epidural abscess in 4 (13.3%), and psoas abscess in 3 (10%). Although statistically insignificant, the frequency of abscess was higher in the GVO group (P=0.242).

Blood cultures were obtained from all patients before the initiation of antimicrobial therapy. Tissue biopsy was obtained from 21 (70%) patients. Microorganisms were isolated in 10 (33.3%). While the same microorganism was isolated in both blood and tissue cultures in 3 patients (10%), some reproduced in the blood culture alone in 3 patients (10%), and in the tissue culture alone in 4 patients (13.3%). The microorganisms isolated in blood cultures included methicillin-resistant coagulase-negative staphylococci (MR CoNS) in 2 (6.7%), methicillin-sensitive coagulase-negative staphylococci (MS CoNS) in 1 (3.3%), methicillin-sensitive *S. aureus* (MSSA) in 1 (3.3%), *E. coli* in 1 (3.3%), and *P. aeruginosa* in 1 (3.3%). Microorganisms isolated in tissue biopsy were *M. tuberculosis* in 2 (6.7%), *P. aeruginosa* in 2 (6.7%), *Enterobacter cloaca complex* in 1 (3.3%), MSSA in 1 (3.3%), and *E. coli* in 1 (3.3%) (Table 2).

Table 2: Culture results of VO cases

Sampling status	Pyogenic VO (n=22) Value (%)	Granulomatous VO (n=8) Value (%)	Total VO (n=30) Value (%)
Patients with blood cultures	22 (100)	8 (100)	30 (100)
Patient with growth in blood culture	6 (27.2)	0	6 (20)
-MSSA	1 (4.5)	-	1 (3.3)
-MS CoNS	1 (4.5)	-	1 (3.3)
-MR CoNS	2 (9.1)	-	2 (6.7)
- *E. coli*	1 (4.5)	-	1 (3.3)
- *P. aeruginosa*	1 (4.5)	-	1 (3.3)
- Culture negative	16 (72.7)	8 (100)	24 (80)
Patients with tissue culture	17 (77.2)	4 (50)	21 (70)
Patients with growth in tissue culture	5 (22.7)	2 (25)	7 (23.3)
-MSSA	1 (4.5)	-	1 (3.3)
- *E. coli*	1 (4.5)	-	1 (3.3)
-*Enterobacter cloaca complex*	1 (4.5)	-	1 (3.3)
- *P. aeruginosa*	2 (9.1)	-	2 (6.7)
- *M. tuberculosis*	-	2 (25)	2 (6.7)
-Culture negative	12 (54.5)	2 (25)	14 (46.6)
-No review	8 (36.4)	5 (62.5)	13 (43.3)

MR CoNS: methicillin-resistant coagulase-negative staphylococci, MSSA: methicillin sensitive S. aureus, MS CoNS: methicillin sensitive coagulase negative staphylococcus, VO: vertebral osteomyelitis

Tissue biopsy samples were also examined histopathologically. Exudative inflammation was reported in 8 (26.7%), chronic granulomatous inflammation in 2 (6.7%), non-specific inflammation in 2 (6.7%), and no specific inflammation in 5 (16.7%).

WBC, CRP, ESR, PCT and IL-6 values were measured in 19 of the patients in the PVO group at baseline and at the 2nd, 4th, and 8th weeks of treatment. They were measured again at week 12 in 3 patients with longer duration of treatment, and at week 24 in 2 patients. In the GVO group, they were measured at baseline, and at the 2nd, 4th, 8th, 12th and 24th weeks of the treatment, since the duration of treatment in all patients was 24 weeks.

While baseline WBC, ESR and IL-6 levels were insignificantly higher in the PVO group than in the GVO group (p=0.197, p= P=0.851, and p=0.963, respectively), CRP and PCT levels were insignificantly higher in the GVO group (p=0.511, and p=0.083, respectively).

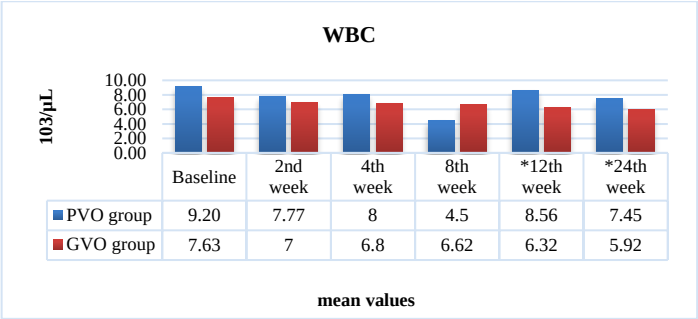
Inter- and intragroup comparisons of baseline WBC, CRP, ESR and IL-6 values and at each follow-up week were conducted. WBC values of the patients in the GVO group gradually and insignificantly decreased each week compared to baseline (P=0.347). In the PVO group, WBC levels did not decrease stably during the follow-up weeks (P=0.441) (Figure 1). CRP levels of the patients decreased at the 2nd, 4th and 8th weeks of the treatment compared to the baseline in both groups (P=0.106, P=0.053, and P=0.009, respectively, in the PVO group, and P=0.050, P=0.025, and P=0.018, respectively, in the GVO group). ESR levels decreased each week, in accordance with the clinical response in both groups compared to baseline (P=0.211, P=0.476, and P=0.025, respectively, in the PVO group, and P=0.036, P=0.012, and P=0.012, respectively, in the GVO group). The decrease between the 4th and 8th weeks of treatment in the PVO group when compared to other follow-up weeks was significant (P=0.005). While there was no difference in WBC and CRP values between the two groups in the same weeks, mean ESR values at weeks 4th and 8th were lower in the GVO group compared to the PVO group (P=0.039 and P=0.027, respectively).

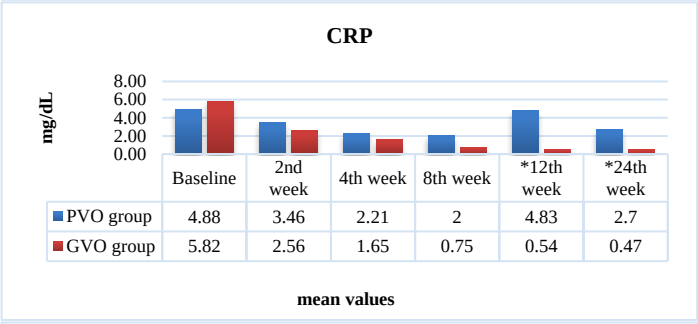
In the GVO group, PCT values decreased gradually at the 2nd, 4th, and 8th weeks of the treatment. In the PVO group, the mean PCT value increased in the 2nd week of the treatment compared to baseline and decreased in the 4th and 8th weeks. In this group, the decrease between the 2nd and 4th weeks and the 2nd and 8th weeks of the treatment was significant (P=0.001, P=0.003). IL-6 levels gradually and insignificantly decreased in the 2nd, 4th, and 8th weeks of treatment in both groups (P=0.069). The PCT values significantly differed between the GVO and PVO groups at week 4 (P=0.009).

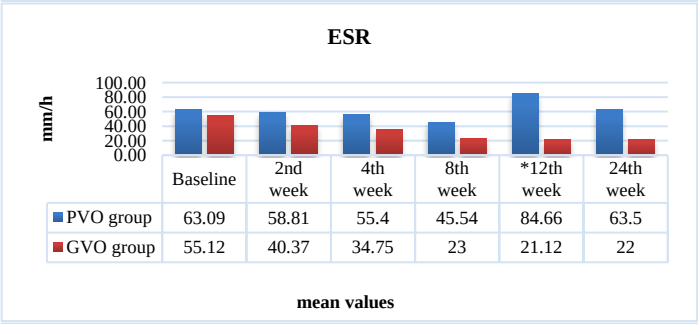
The mean total follow-up time of the patients was 13.4 (7.6) weeks. GVO cases were treated and followed for 24 weeks. Patients with PVO were given 2-4 weeks of intravenous antibiotherapy, followed by oral antibiotherapy. The total duration of antibiotherapy was 8 weeks in 19 of these patients (86.4%), 12 weeks in 1 (4.5%) patient and 24 weeks in 2 (9.1%) patients. The mean duration of intravenous antibiotherapy was 2.9 (2.2) weeks, and the total duration of antibiotherapy and follow-up time was 9.6 (4.72) weeks.

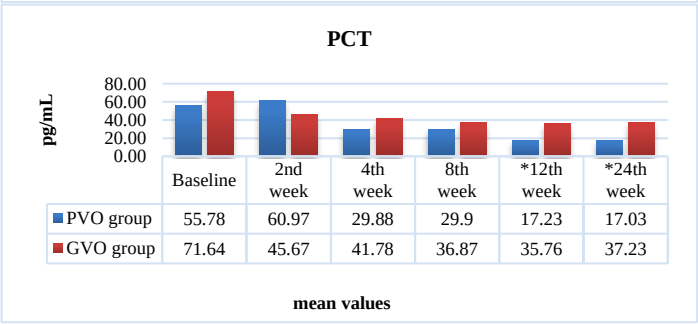
Twenty-eight patients (93.3%) were cured with medical and/or surgical treatments; 1 (3.3%) patient was considered unresponsive, and 1 (3.3%) patient had relapse.

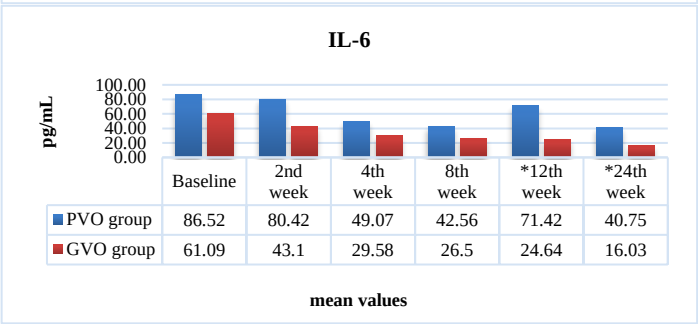
Figure 1: Comparison of baseline and follow-up laboratory parameters of PVO and GVO cases











WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IL: interleukin, PCT: procalcitonin, VO: vertebral osteomyelitis

P-values for mean WBC values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.197, *P*=0.159, *P*=0.241, *P*=0.044.
P-values for mean CRP values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.511, *P*=0.336, *P*=0.540, *P*=0.070.
P-values for mean ESR values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.851, *P*=0.189, *P*=0.039, *P*=0.027.
P-values for mean PCT values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.083, *P*=0.851, *P*=0.009, *P*=0.214.
P-values for mean IL-6 values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.963, *P*=0.205, *P*=0.174, *P*=0.146.

*In the PVO group, 19 of 22 patients were treated for 8 weeks and laboratory tests were performed at 0, 2, 4, 8 and 12 weeks of treatment. The 12th week results of treatment included only 3 patients, and the 24th week results included only 2 patients. Therefore, only mean values are given for these weeks and no comparison with the GVO group was made.

Discussion

There is a surge in the incidence of VO due to the development in diagnostic modalities, increasing number of surgical interventions and the widespread use of immunosuppressive treatments. Although the mortality risk due to the disease is low, severe back pain and neurological sequelae can seriously disrupt the daily life of the patients. Multidisciplinary approach of infectious diseases and clinical microbiology specialists, neurosurgeons, radiologists and orthopedists have a great importance in the follow-up and treatment of the disease. The basis of treatment is the identification of the causative agent and antibiotic sensitivity, for which a tissue culture is required. However, usually, nor the surgeon, neither patient wants the biopsy, and the samples taken are not sent to the laboratory properly. As a result, the agent cannot be detected [3,7]. In these cases, laboratory parameters in follow-up are of great importance for patient management. In our study, we used PCT and IL-6 markers in addition to WBC, CRP and ESR, all of which are used in daily practice to evaluate the efficacy of antibiotherapy. This is the first study in the literature which evaluated PCT and IL-6 comparatively with CRP and ESR in VO treatment follow-up.

Many microorganisms can cause VO, such as pyogenic bacteria, *Brucella spp.*, TB bacillus, fungi, and parasites [3,7]. In the study of Mete et al. [18], among 100 spontaneous VO cases, 44% were caused by pyogenic bacteria, 32%, by TB bacillus and 24%, by *Brucella spp*. In another study by Kaya et al. [19], causative agents were pyogenic bacteria in 61.6% of the patients, Brucella spp. in 33.6%, and TB bacillus in 4.7%. In our study, 73.3% of the patients had PVO, 20% had brucellosis, and 6.7% had TB. The causative microorganisms were similar to those reported in the literature.

S. aureus is the most common cause of PVO. Other causative agents include GNB, other Gram-positive cocci and less often, anaerobes [7]. In the study of Chang et al. [20], *S. aureus* was the most common bacterium (72%), and GNB were found in 32.6%, *Streptococcus spp.* in 21.2%, Coagulase negative staphylococci (CoNS) in 7.2%, *Enterococcus spp.* in 5.2%, anaerobes in 4.8%, and other Gram-positive cocci, in 1.6%. The most common GNB were *E. coli*, *Klebsiella spp*. and *Salmonella spp.*. Eren Gok et al. [21] collected urine and stool cultures, as well as blood and tissue samples for microbiological sampling, and determined the agent in 42%. The most common causative agent was *S. aureus*, followed by GNBs, including *E. coli*, *Klebsiella spp.* and *Salmonella spp.*. In our study, blood and tissue cultures were used for microbiological sampling. The causative agent could be identified in 10 patients' (33.3%) blood and tissue cultures: It was MR CoNS in 2 patients (6.7%), MS CoNS in 1 patient (3.3%), MSSA in 1 patient (3.3%), *E. coli* in 1 patient (3.3%), *P. aeruginosa* in 2 patients (6.7%), and *E. cloaca complex* in 1 patient (% 3.3) and *M. tuberculosis* in 2 patients (6.7%). The distribution of the agents in our study was compatible with the literature (40% Gram positive, 40% Gram negative, 20% TB).

A 2010 review by Gouliouris et al. [7] stated that the rate of tissue biopsy for the diagnosis of VO was between 19-100%, and the rate of agent detection in biopsies varied between 43-78%. In the study of Lora-Tamayo et al. [22], culture

positivity was detected in only 19% of the patients with CT-guided tissue biopsy. In our study, 70% of the patients underwent intraoperative tissue biopsy and pathogenic microorganisms were isolated in 23%. Our results are similar to those in the literature.

The definitive diagnosis of VO is made by microbiological isolation. However, the diagnosis becomes difficult due to the low rates of tissue biopsy and isolation of agents in tissue cultures. So, the most important parameters used in diagnosis of VO are laboratory biomarkers [23]. ESR has high sensitivity and low specificity in the diagnosis of infection. The elevation of ESR is independent of the severity of the infection and the age of the patient. Most studies showed that it is elevated in more than 90% of patients with VO, and the mean value ranges between 43 to 87 mm/h. CRP is an important marker in the diagnosis of VO [3, 7]. In the literature, it is reported that both markers are 84% sensitive separately in the diagnosis of VO [24]. Their combined use yields a sensitivity of 94-100%, but specificity is low [3]. WBC count is not a sensitive marker in the diagnosis of spinal infection. Although a very slight increase is usually observed, it is within the normal range in the elderly population and immunocompromised patients. Elevated WBC levels were found in only 42.6% of PVO cases [24].

In our study, the mean baseline WBC levels were within normal limits, and those of PVO patients were higher than those of GVO patients. Leukocytosis was detected in 31.8% of the patients with PVO and in 12.5% of the patients with GVO. However, this difference was not statistically significant. The mean values were 9209.09 µL in the PVO and 7637.5/µL in the GVO groups. These results are compatible with literature data.

In the PVO group, 95.5% of the patients had elevated CRP and 100% had elevated ESR. The mean values for CRP and ESR were 4.88 mg/dl and 63.09 mm/h, respectively. In the granulomatous group, CRP and ESR elevation were detected in 100% of the patients. Mean values for CRP and ESR were 5.83 mg/dl and 55.13 mm/h, respectively. No significant difference was found between the groups. According to our data, ESR and CRP are more useful biomarkers than WBC count for diagnosing VO, regardless of the etiology.

PCT is a valuable biomarker used in the diagnosis and treatment follow-up of infections [9, 25]. There were a few studies in the literature in which PCT was used in the diagnosis and follow-up of VO. There are also studies in which the diagnostic value is investigated mostly in extremity osteomyelitis and prosthetic infections and compared with other inflammation markers [14, 17]. In the study of Maharajan et al. [14], PCT was a very sensitive and specific marker in the diagnosis of acute osteomyelitis and septic arthritis when the cut-off was 0.4 ng/ml. Jeong et al. [26] detected PCT elevation in 73% of all patients diagnosed with spinal infection, but most patients with PCT elevation had a coinfection. In a study by Maus et al. [27], two groups with PVO and disc herniation were compared. Serum CRP values were increased in all except 2 cases in the infection group, while PCT value increased in only 1 patient with infection, but not in any patient in the disc herniation group. In this study, it was concluded that PCT is not a suitable marker for the diagnosis of spinal infections. In a study by Yoon et al. [23] comparing pyogenic and TB VO cases, serum PCT levels were insignificantly higher in the PVO group. In our study, only one of our patients had PCT>200 pg/ml, which was the cut-off value. Our results may contribute to the contradictory literature data that PCT level cannot be used in the diagnosis of VO. However, it does not seem possible to reach a definite conclusion, since there was no control group in our study and the cut-off could not be determined. In this study, we did not create a control group, as our aim was not to determine the value of PCT and IL-6 biomarkers in diagnosis, but to investigate their usability in treatment follow-up.

Although there are studies on extremity osteomyelitis and prosthesis infection in the literature, we could not find any study in which IL-6 was used in the diagnosis and treatment follow-up of VO. In a study conducted in Germany in 2014, IL-6 levels in the serum and synovial fluid samples of patients with prosthesis infection and aseptic loosening were compared and IL-6 levels in both body fluids were more sensitive for diagnosis than serum WBC, ESR and CRP levels [28]. In a study of Van Asten et al. [29] on patients with diabetic foot infection, IL-6 was measured at baseline, and at the 3rd and 6th weeks, which revealed that it decreased in parallel with the treatment response in patients. It was concluded that it is a valuable parameter to use in treatment follow-up. In a study investigating the value of serum inflammation markers in chronic osteomyelitis, IL-6 was the most sensitive marker with a rate of 72.8% among WBC, CRP, ESR, PCT, IL-6 and TNF-a [30]. In a study of Bottner et al. [31] IL-6 was defined as the most sensitive laboratory parameter in patients with prosthesis after CRP with a rate of 95% when the cut-off value was 12 pg/ml. In the study of Glehr et al. [32] on prosthetic infections, when the cut-off value for IL-6 was 2.55 pg/mL, the sensitivity was 92% and the specificity was 59%. In our study, IL-6 levels were above 3 pg/ml, which was considered the cut-off value, in all 30 patients. There was no difference between patients with PVO and GVO. Although we cannot determine the cut-off value because there is no control group, the detection of elevated IL-6 levels suggests that IL-6 may be a useful biomarker in the diagnosis. Our data also seems compatible with literature.

In our study, WBC decreased by 16% in the PVO group and 13% in the GVO group compared to baseline at the 8th week of treatment, and paradoxically increased in the PVO group at 4th week. Therefore, we think that this is not a valuable parameter in VO follow-up, similar to the literature.

In this study, a decrease in CRP and ESR values was detected in all patients in parallel with the treatment response. ESR response was slower in the PVO group. In PVO patients, only a 12% decrease was detected in ESR values compared to pre-treatment values at the 4th week of treatment while in GVO patients, a 58% decrease was noted. In the PVO patient group, 60% decrease in CRP values at the 8th week of treatment compared to baseline was a significant parameter in terms of showing clinical improvement in patients.

Although a paradoxical increase was observed in the PCT values of the PVO group in the 2nd week compared to baseline, a rapid, significant decrease was observed in the 4th and 8th weeks. In the GVO patient group, the gradual decrease in PCT in parallel with the treatment response during all follow-up weeks was an indicator predicting clinical improvement. Based on our data, PCT can be used to monitor treatment follow-up in

patients with VO. However, according to the results of the study, it cannot be said whether PCT is a more useful biomarker for treatment follow-up than CRP and ESR. For more precise results, it would be appropriate to conduct a study involving more patients.

IL-6 levels were decreased in both groups in line with the treatment response. Although there was no statistically significant difference between baseline and the 2nd, 4th and 8th weeks of treatment in both groups, the decrease in IL-6 levels in parallel with the clinical response suggests that this biomarker can be used to monitor the treatment response. The fact that these decreases are more stable than CRP and ESR suggests that IL-6 may be a more useful parameter in the treatment follow-up.

Limitations

This was a single center study with a small number of patients and there was no control group.

Conclusion

Isolation of a microorganism is not always possible. In our study, the causative agent was isolated in only one third of the patients. Regardless of the etiology, the most sensitive markers in the diagnosis of VO were CRP, ESR and IL-6. PCT, detected above the threshold value in only 1 patient at baseline, was not a useful marker in the diagnosis of VO. The levels of CRP, ESR, IL-6 and PCT change in parallel with the clinical response in VO and are useful parameters for follow-up. A more stable decrease in IL-6 levels suggests that it is a more valuable biomarker that can be used in follow-up.

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Postoperative results and the effects of extended partial laryngectomy on the quality of life

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Ethics Committee Approval
The study was approved by Gaziantep University Clinical Research Ethics Committee on 21 March 2016 with the decision number 2016/90. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Larynx cancers account for 2-5% of all malignancies worldwide. With early diagnosis, radiotherapy or a partial laryngectomy may help preserve voice and laryngeal functions and reduce morbidity. This study aimed to evaluate how laryngeal functions, voice, and life quality were affected in larynx cancer patients after partial and extended partial laryngectomy.

Methods: The patients who were diagnosed with larynx cancer and underwent partial (supraglottic laryngectomy (SGL), supracricoid laryngectomy (SCL)) or extended partial laryngectomy (extended supraglottic laryngectomy (ESGL) and extended supracricoid laryngectomy (ESCL)) between May 2010 and December 2015 in the otorhinolaryngology clinic of a Training and Research Hospital were included in this study. A questionnaire comprising three forms was filled in by these patients. Voice quality, duration of hospitalization, time until removal of the nasogastric tube, location of the tumor, time of decannulation, swallowing, and cough were compared with regards to the types of laryngectomies.

Results: Our study began with 102 patients who had a partial laryngectomy; however, twelve who eventually had to undergo a total laryngectomy were excluded. Of the remaining 90 patients, 67 filled out our questionnaire. Functional score (FS), social functional score (SFS), symptom score (SS), fatigue score (FAS), general health score (GHS), and swallowing symptoms score (HNSW) were calculated and compared. These scores did not differ with the types of laryngectomies. In terms of voice quality, there were significant differences between ESCL-SGL, SCL-SGL, ESGL-SGL groups (P=0.001, P=0.004, and P=0.004, respectively).

Conclusion: Despite numerous changes in swallowing physiology and larynx anatomy after partial and extended partial laryngectomy, swallowing function is restored, and the patients can lead a healthy life.

Keywords: Larynx cancer, Life quality, Voice

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Introduction

Larynx cancers, which account for 2-5% of all malignancies worldwide and in the Turkish population, can be diagnosed early with the increasing use of endoscopy and stroboscopy. Good outcomes are expected for survival and quality of life with appropriate treatment. With early diagnosis, radiotherapy or a partial laryngectomy may help preserve voice and laryngeal functions, reduce morbidity, and increase the quality of social life. In advanced tumors, however, preserving laryngeal functions takes a backseat, and radical methods such as a total laryngectomy are employed [1, 2].

The traditional goal with cancer treatment is to eliminate the disease and prolong the patient's life. Today, treatments are aimed at reintegrating the patient back into social and economic life, strengthening their social bonds with society, and improving their quality of life so they feel happy about themselves and their lives. Quality of life includes all situations and factors that affect the individual. When planning cancer treatments, these factors should be well-considered and there should be an awareness about the impact of the disease and the treatment on people's lives. Many studies have been conducted to measure and evaluate the efficacy of these treatments [3-6].

After the World Health Organization defined health as "not only the absence of a disease or disability but also as a complete state of peace and well-being, physically, mentally and socially" in 1948, the concept of quality of life gained increasing importance in healthcare practice with a commensurate increase in research assessing health-related well-being [3]. The first studies for assessing the quality of life were published in 1973. In recent years, their number gradually increased, especially the cost-benefit analysis of novel programs and treatments [7, 8].

To measure the effects of treatment on quality of life, several multidimensional questionnaires, as well as questionnaires for the evaluation of head and neck cancers alone, were developed. We used EORTC QLQ-C30 (Quality of Life Questionnaire) and QLQ-H & N35 (Quality of Life Questionnaire for Head and Neck Cancer) developed by the European Organization for Research and Treatment of Cancer (EORTC) to evaluate the quality of life of cancer patients, along with a questionnaire developed in our clinic [9]. This study aims to compare the cancer stages of patients who underwent partial and extended partial laryngectomy for larynx cancer in our clinic, evaluate the surgical outcomes and their quality of life, and perform survival analysis.

Materials and methods

This study was conducted between May 2010 and December 2015 on 102 patients who underwent surgery and additional radiotherapy as needed for larynx cancer at the Training and Research Hospital, Otorhinolaryngology & Head and Neck Surgery Clinic.

Inclusion criteria were as follows:

1. Patients diagnosed with SCC after preoperative biopsies
2. Those who underwent surgery as primary treatment
3. Patients followed up at our clinic
4. Patients who underwent postoperative radiotherapy as needed.

Our study was approved by Gaziantep University Clinical Research Ethics Committee on 21 March 2016 with the decision numbered 2016/90.

The preoperative and postoperative follow-up data of patients were recorded in our data collection system. Intraoperative data were recorded in our clinic's ledger of surgeries. Patients or their relatives were contacted via the telephone numbers in our records and called in for a medical examination. After routine examination, they were given detailed information about the study.

After filling out the patient information and consent forms, the patients proceeded to complete the form, consisting of the three following parts:

1) EORTC QLQ-C30 Version 3.0 Turkish, which is a quality-of-life scale for cancer patients (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire) [4]
2) EORTC QLQ-H&N35 Turkish, which is a head and neck cancer scale (European Organization for Research and Treatment of Cancer, Questionnaire module to be used in Quality-of-Life assessments in Head and Neck Cancer) [4]
3) A questionnaire consisting of questions about the quality of life, designed in our clinic.

The basic demographic and clinical data of the patients were evaluated. The information was obtained from the patients and their files. The included parameters were age and gender of the patients, smoking habits, alcohol use, tumor sites, TNM and stage of the tumor, surgical treatments, postoperative complications, postoperative hospitalization, time until oral feeding, decannulation time, histopathological changes in the tumor and patients' medical histories.

Postoperative radiotherapy was recommended for the patients with a T4 tumor, bone/cartilage invasion, invasion of the soft tissues of the neck, perineural invasion, vascular invasion, multiple positive lymph nodes, extracapsular spread in the lymph node, and a subglottic extension of more than 10 mm in the anterior region and 5 mm in the posterior region [10-12].

Partial laryngectomy included supraglottic laryngectomy (SGL) and supracricoid laryngectomy (SCL), while extended partial laryngectomy comprised extended supraglottic laryngectomy (ESGL) and extended supracricoid laryngectomy (ESCL).

After the patient information and consent forms, the patients also filled out the three questionnaires for assessment and comparison of their life quality.

The EORTC QLQ-C30, Version 3.0 (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire) is not a specific questionnaire for larynx cancer, but it is still a commonly used quality of life questionnaire for cancer patients worldwide [13].

The scale for head and neck cancer, EORTC QLQ-HN35 (European Organization for Research and Treatment of Cancer, Questionnaire module to be used in Quality-of-Life assessments in Head and Neck Cancer), was designed as an additional questionnaire to the EORTC QLQ C-30 to better assess the quality of life of patients with head and neck cancer [14, 15].

The questionnaire of 15 questions developed by our clinic included queries concerning the following: The decannulation process for patients who underwent laryngectomy, the duration until removal of the nasogastric feeding tube (NG), postoperative complications, postoperative voice quality, nasal obstructions, headaches, whether the patient coughed during oral feeding after the removal of the NG tube, post-nasal drips, length of hospitalization, wound site infections, whether the patient contracted a lung infection after surgery and impairment in their sense of smell.

Statistical analysis

Conformity to normal distribution of the numerical data was tested with the Shapiro–Wilk test. The Mann-Whitney test was used in the comparison of non-normally distributed variants between two groups, and the Kruskal Wallis test was used to compare the non-normally distributed variants between four groups. The relationship between categorical variables was assessed using the Chi-Square test. SPSS 22.0 package software was for analysis. $P<0.05$ was considered statistically significant.

Results

A total of 102 patients treated in our clinic for larynx cancer between May 2010 and December 2015 were included in the study. The mean age of the patients was 56.1 (range 29-70) years. Ninety-four of the 102 patients were male and 8 were female. Of these, SGL was performed in 51 patients, SCL, in 24 patients, ESGL, in 19 patients and ESCL, in 8 patients (Table 1). These patients also underwent neck dissection. Only one patient who received preoperative radiotherapy did not have a neck dissection performed.

Table 1: Demographic characteristics of the patients included in the study

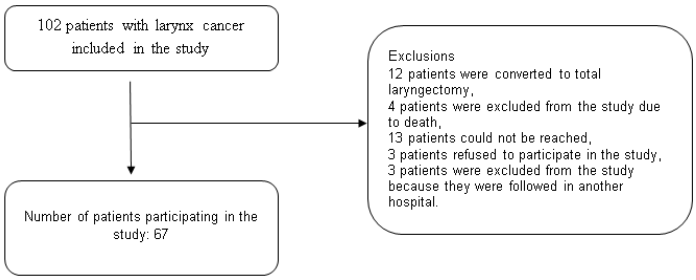
	Number (n)	Percentage (%)
Sex		
Female	8	7.84
Male	94	62.16
Distribution of patients by age group		
20-30	1	0.98
31-40	1	0.98
41-50	25	24.50
51-60	43	42.15
61-70	32	31.37
Types of laryngectomies		
SGL	51	50
SCL	24	23.52
ESGL	19	18.62
ESCL	8	7.84
Total	102	100

SGL: supraglottic laryngectomy, SCL: supracricoid laryngectomy, ESGL: extended supraglottic laryngectomy, ESCL: extended supracricoid laryngectomy.

Disease staging was performed postoperatively. Eighteen patients were assessed as stage I, 39 patients as stage II, 12 patients as stage III, 11 patients as stage IVa, and 7 patients as stage IVc.

Of 102 patients included in the study who underwent partial laryngectomy, 12 eventually underwent total laryngectomy and were excluded. Six of these patients underwent total laryngectomy due to relapse while the remaining had a total laryngectomy due to difficulties with aspiration and swallowing. Sixty-seven of the remaining 90 patients participated in our survey. Three of the twenty-three patients could not be evaluated due to being followed up at another hospital, 4 died, 13 could not be reached and 3 refused to participate in the survey (Figure 1). Of the sixty-seven patients interviewed, 33 had SGL, 12 had SCL, 15 had ESGL and 7 had ESCL (Table 2).

Figure 1: Flow diagram of the study



Sixty-seven patients were first divided into two groups, as those who had a partial and extended partial laryngectomy, and a further classification was made based on these groups. The functional score (FS), the social function score (SFS), the symptom score (SS), the fatigue score (FAS), the general health score (GHS), and the swallowing symptoms score (HNSW) were calculated and compared (Table 3).

Table 2: Data of patients who participated in the survey

	Number (n)	Percentage (%)
Patients Participating in the Survey		
Those who had partial laryngectomy	45	67.2
Those who had extended partial laryngectomy	22	32.8
Type of laryngectomy		
ESCL	7	10.4
ESGL	15	22.4
SCL	12	17.9
SGL	33	49.3
Lung infection		
Those who had the infection	12	17.9
Those who did not have an infection	55	82.1
Total	67	100

SGL: supraglottic laryngectomy, SCL: supracricoid laryngectomy, ESGL: extended supraglottic laryngectomy, ESCL: extended supracricoid laryngectomy

Table 3: Comparison of quality-of-life scores according to laryngectomy types

	Number (n)	FS mean (SD)	SFS mean (SD)	SS mean (SD)	FAS mean (SD)	GHS mean (SD)	HNSW mean (SD)
Those who had partial laryngectomy	45	79.24 (18.9)	81.48 (28.91)	21.70 (20.66)	31.31 (24.46)	55.74 (24.98)	29.62 (25.34)
Those who had extended partial laryngectomy	22	78.18 (20.01)	83.33 (26.72)	19.69 (17.91)	32.82 (26.22)	54.54 (16.81)	34.84 (22.36)
P1		0.881	0.865	0.857	0.912	0.813	0.236
P2		0.536	0.536	0.592	0.837	0.482	0.432
P3		0.623	0.784	0.938	0.926	0.324	0.530

FS: functional score, SFK: social functional score, SS: symptom score, FAS: fatigue score, GSS: general health score, HNSW: swallowing symptoms score, SD: standard deviation, P1: p values for partial laryngectomy and extended partial laryngectomy groups, P2: p values for extended supracricoid laryngectomy and supracricoid laryngectomy groups, P3: p values for extended supraglottic laryngectomy and supraglottic laryngectomy groups, $P<0.05$ statistically significant

The FS ($P=0.881$), GHS ($P=0.813$), and all quality-of-life scores (Table 3) were similar between the groups who underwent partial and extended partial laryngectomy.

The patients who underwent laryngectomy were compared in terms of the food they consumed and their cough severity. They were asked to respond to questions concerning the relationship between the food they consumed, both solid and liquid, and their coughing using the options "yes", "no", "sometimes". Solid and liquid foods were evaluated separately according to the different types of laryngectomy surgeries performed on the patients. The groups were similar in terms of cough severity during solid ($P=0.053$) and liquid ($P=0.308$) food consumption (Table 4).

Twelve patients had one or more lung infections and received treatment because of aspiration during eating and drinking. Patients who had a partial laryngectomy and a lung infection due to the food they consumed were compared based on different types of laryngectomy surgeries they had undergone, and no statistically significant differences were found ($P=0.505$) (Table 4).

Table 4: Relationship between foods and coughing

		Types of laryngectomies				
		ESCL	ESGL	SCL	SGL	*P*-value
Relationship between solid food and coughing	Sometimes	1	4	3	15	
	Yes	3	7	3	3	0.053
	No	3	3	6	15	
Relationship between liquid food and coughing	Sometimes	3	3	5	16	
	Yes	3	9	4	8	0.308
	No	1	2	3	9	
Lung infection	Those who had the infection	2	1	2	7	0.505
	Those who did not have an infection	5	14	10	26	
Total number of patients		7	15	12	33	

SGL: supraglottic laryngectomy, SCL: supracricoid laryngectomy, ESGL: extended supraglottic laryngectomy, ESCL: extended supracricoid laryngectomy. $P<0.05$ statistically significant

In the survey, patients were asked to appoint scores on a scale of 1 to 7 to determine voice quality, where 1 point indicated "very bad", and 7 points indicated "perfect". The mean voice quality score was higher in patients who underwent SGL compared to the others (SGL mean score: 4.6). The mean score was lower in patients who underwent an extended laryngectomy compared to the other group (mean scores respectively ESGL: 3.4, SCL: 3.2, ESCL: 2.7).

Significant differences were found between the ESCL-SGL, SCL-SGL, and ESGL-SGL groups in terms of voice quality scores (P=0.001, P=0.004, P=0.004, respectively). This was attributed to the preservation of both vocal cords in SGL.

Based on different types of laryngectomy surgeries, the patients were compared about decannulation time and the length of time elapsed until the removal of the NG tube. The decannulation time and duration until NG tube removal were insignificantly longer in patients who underwent ESCL compared to patients who had other types of laryngectomies (Table 5).

Table 5: Decannulation time and length of time spent with an NG tube

	Types of laryngectomies				
	ESCL	ESGL	SCL	SGL	*P*-value
Decannulation time (day)	16.85	15.27	16.25	15.15	0.422
Length of time spent with an NG tube (day)	39	38.07	37.45	35.06	0.991

SGL: supraglottic laryngectomy, SCL: supracricoid laryngectomy, ESGL: extended supraglottic laryngectomy, ESCL: extended supracricoid laryngectomy, NG: nasogastric tube, $P<0.05$ statistically significant.

Discussion

In this study, we evaluated the surgical results of 102 patients who underwent partial laryngectomy for larynx cancer, and the quality of life of 67. The mean age of the patients was 56.1 years (29-70 years). The scores were similar to those reported in most studies [12, 16, 17] but less than some [18]. In recent years, the number of younger patients admitted to our clinic increased. While the rate of females in our study was 7.8%, those reported by Portal et al. [19] and Gok et al. [20] were 3.2% and 4.0%, respectively.

Park et al. evaluated the functional outcomes of 116 patients who underwent partial laryngectomy due to larynx cancer between 2009-2013 [21]. The patients were followed up over at least 12 months and divided into two groups, SCL (n=84) and ESCL (n=32), according to arytenoid resection. Among those that underwent SCL and ESCL, the mean decannulation times were 16.83 days and 23.27 days, respectively, while the time passed until NG tube removal was 24.19 days and 27.33 days, respectively. The two groups were similar in terms of eating routines after NG tube removal and significantly different with regards to decannulation time and rate of aspiration pneumonia. We also found no differences between our ESCL and SCL groups in terms of eating routines. This study supports our findings.

Bron et al. conducted a study to evaluate the effect of arytenoid resection on patients who underwent SCL and reported that arytenoid resection does not cause any significant difference regarding the time a patient spends with an NG tube. They concluded that a simple resection of the arytenoid does not impact swallowing in the early postoperative phase [22].

Akbas et al. evaluated the functional outcomes of 46 patients who underwent supracricoid laryngectomy. The mean decannulation time was 20 days in the group where both arytenoids were preserved, and 41 days in the group that had just one arytenoid resected. The mean time spent with an NG tube was 21 days (9-60 days) in the group where both arytenoids were preserved; while it was 40 days in the group who had one arytenoid resection [23]. In the study of Yuce et al., the decannulation time was 40.2 days in the patient group with a single arytenoid and 20.8 days in the patient group with both arytenoids preserved. The length of time spent with an NG tube was 18.4 days in the patient group with a single arytenoid and 8.8 days in the patient group with both arytenoids preserved. In this study, the differences between the two groups were statistically significant [24]. We found no significant differences between our SCL and ESCL patients in terms of decannulation time and time until NG tube removal.

In partial laryngectomies, aspiration-related complications are one of the most important postoperative complications. A possible incidence of aspiration delays decannulation and the transition to oral feeding, resulting in an extension of hospitalization times and cost increase [25-27]. Başerer et al. [28] found postoperative aspiration rates affecting oral nutrition to be 6% while it was 5% according to Oz F. et al. [29]. Ulusan et al. [30] have shown that the incidence of aspiration goes up in cases where the FEV1 value (Forced Expiratory Volume in 1 second) lies below 75% in a lung function test. Therefore, in patients scheduled to undergo a laryngectomy, preoperative PFTs (Pulmonary Function Test) and seeking the opinion of a chest diseases specialist are recommended.

Mc Connel et al. analyzed the swallowing function in patients after supraglottic laryngectomy and found three aspiration-causing factors. These are decreased and delayed laryngeal elevation and weak laryngeal-lingual approximation [31]. Since a standard supraglottic laryngectomy performed during the resection of a supraglottic carcinoma protects the arytenoids and vocal cords, the larynx can perform its protective function. However, some patients lose their epiglottis, and arytenoids and vocal cords need to do additional work to cover the laryngeal sphincter. The possible complications after a supraglottic laryngectomy are chronic aspiration due to glottis insufficiency, hyposensitivity caused by incision of the superior laryngeal nerve, and insufficient elevation of the larynx to the root of the tongue. After an extended supraglottic laryngectomy, which includes part of the root of the tongue, the arytenoid cartilage, the aryepiglottic fold, and/or the piriform sinus, and swallowing problems intensify, and aspiration problems may

arise. Resection of the root of the tongue can damage the 12th cranial nerve and cause hypomobility of the root of the tongue which can impair the root of the tongue's ability to pull backward [32]. In our study, coughing after solid and liquid food intake was higher in patients who had ESGL and ESCL than in those who had SGL and SCL. These patients also took longer to switch to oral feeding in the post-operative period. Patients were thought to tolerate this condition over time.

In a study conducted by Gallo et al. [33], prognostic factors in pneumonia developing after supraglottic and supracricoid laryngectomy were investigated. In a series of 416 cases, pneumonia occurred in 73. Three of these patients died of respiratory arrest and sepsis. Of the 73 patients, 26 had early-stage pneumonia and 44 had late-stage pneumonia. The number of cigarettes smoked, body mass index, lung diseases before surgery, age, gender, preoperative blood gas values, tumor stage, and type of surgery were assessed as potential risk factors for postoperative pneumonia. In the study, a stage III-IV disease, a history of lung diseases, a preoperative hemoglobin level of less than 14, and a preoperative pO_2 level of less than 90 in the blood gas had prognostic significance. Early postoperative pneumonia was associated with patients over 60 years of age and those with a body mass index>30 kg/m^2. Forty-two of 70 patients who had pneumonia had growth in their sputum culture. The most isolated pathogen was Staphylococcus aureus. More than one species was isolated in 22 patients. In the culture analysis, no significant differences were found between the groups in terms of microorganisms [33]. In this study, the incidence of pneumonia in the postoperative period was 16.8%, which was similar to the finding in our study (17.9%).

Woisard et al. [34, 35] examined the swallowing functions of patients who had supraglottic and supracricoid laryngectomies. It was concluded that edema in arytenoids may contribute to laryngeal occlusion and that food accumulating around the arytenoid may increase the risk of aspiration.

Philippe et al. conducted a study showing the postoperative functional results in 190 patients who had a supracricoid partial laryngectomy with cricohyoidopexy [36]. Normal swallowing was achieved in the first postoperative month in 68.1% of the patients (128/188). Grade 1-2 aspiration was observed in 23.4% (44/188) between the 1st and 4th months. Grade 1-2 aspiration was treated in conjunction with physiotherapy and swallowing rehabilitation. Grade 1-2 aspiration was reported to occur due to old age, repositioning of the piriform sinuses and inferior constrictor muscles, disarticulation of the arytenoid cartilage, and extended insertion of the tracheostomy tube. Pneumonia due to aspiration (grade 3 aspiration) was seen in 8.5% (16/188) of the patients. Aspiration-induced pneumonia was treated by antibiotics and physiotherapy in 13 patients, collagen injection in 1 patient, and temporary gastrectomy in 2 patients. At the end of the first postoperative year, the rate of permanent gastrostomy placement and total laryngectomy due to aspiration was 0.5% (1/188) and 98.4% of the patients (187/190) regained their normal swallowing functions without a gastrostomy. In this study, the early removal of the tracheostomy tube led to the rapid mobilization of the arytenoid cartilage, maintenance of the cough reflex, and prevention of pulmonary infections. It has been argued that early decannulation improves swallowing because the tracheostomy tube reduces laryngeal elevation during swallowing, affecting the sensitivity of the mechanical laryngeal receptors.

Limitations

The small size of our patient group may be a limitation of our study. Future studies with a larger group of patients might well establish the exact relationship of laryngectomy results.

Conclusions

A comparison of the cited studies and the current study reveals that due to the numerous changes in swallowing physiology and anatomy following partial laryngectomies and extended partial laryngectomies, restoration of the swallowing function can also take a long time in some patients. Even in such cases, it can be argued that patients regain most of their swallowing functions and can continue to lead healthy lives.

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The role of urinary kidney injury molecule-1 in monitoring the child with idiopathic microscopic hematuria

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Abstract

Background/Aim: Idiopathic microscopic hematuria is common during childhood, and numerous factors play a role with varying degrees in its etiopathogenesis. We aimed to investigate whether urinary kidney injury molecule-1 level could be a new indicator to detect a possible renal injury that may cause idiopathic microscopic hematuria.

Methods: This prospective case-control study included 38 children between 1-15 years of age who were followed up due to idiopathic microscopic hematuria without hypertension and/or edema and 39 healthy individuals with similar gender distribution. Kidney injury molecule-1, urine culture, microalbumin, calcium, magnesium, uric acid, and creatinine levels in spot urine were measured in both groups. A throat culture and abdominal ultrasound were performed on all those included.

Results: No significant differences were found between the patient and control groups in terms of age, gender, weight, and height ($P>0.05$). Microalbumin, microalbumin to creatinine ratio in spot urine, urinary kidney injury molecule-1 levels, and kidney injury molecule-1 to creatinine ratio were higher among the patients than the controls ($P=0.016$, $P=0.013$, $P=0.001$, and $P=0.001$, respectively).

Conclusion: Urinary microalbumin and kidney injury molecule-1 levels, as well as rates of these two markers to creatinine, may be higher in the children with idiopathic microscopic hematuria. Our findings show that children with microscopic hematuria should be monitored for renal tubular injury and the development of chronic renal disease.

Keywords: Idiopathic microscopic hematuria, Kidney injury molecule-1, Microalbuminuria

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Introduction

Hematuria refers to finding erythrocytes in the urine. This disorder may be visible, as in macroscopic hematuria, or detected by urine analysis, as in microscopic hematuria. Idiopathic microscopic hematuria (IMH) is not associated with any underlying pathology. The prevalence of pediatric hematuria ranges between 1-2% [1]. Persistent asymptomatic IMH was diagnosed in 3690 of 1,203,626 (0.3%) eligible young adults and adolescents [2]. However, hematuria may be one of the early symptoms of renal and systemic pathologies, and in some cases, early diagnosis of the underlying disease may alter its course, such as in acute glomerulonephritis, IgA nephropathy, membranoproliferative glomerulonephritis, hypercalciuria, nephrolithiasis, congenital renal abnormalities, Alport Syndrome, and urinary tract infection [3-5].

Classically, IMH is considered a benign disease associated with glomerular diseases. However, the latest data obtained from clinical and experimental studies demonstrate the negative role of glomerular hematuria on renal disease [6, 7]. Hematuria may cause progression to chronic renal disease through glomerular and/or tubular damage [8, 9]. If microscopic hematuria accompanies macroscopic hematuria, the probability of developing chronic kidney disease increases [8, 10, 11].

Biological markers that may be measured objectively show normal or pathological processes. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein that is produced in proximal tubular cells of the kidney in ischemic and nephrotoxic acute kidney injury (AKI) [11-15]. Some manuscripts report that KIM-1 is a "scavenger receptor" in renal epithelial cell assigned to collect apoptotic material from the tubular lumen [16-18]. The extracellular part of this transmembrane protein is broken down proteolytically and may be detected in the urine. The soluble KIM-1 protein that may be measured in the human urine is approximately 90 kDa [3, 19-21].

In this study, we measured the level of KIM-1, produced by renal tubular cells, which is considered to show a risk of progression to chronic kidney failure in children with IMH. We aimed to detect whether this molecule could determine the prognosis of IMH in terms of renal tubular and/or glomerular damage when compared with healthy children and compared microalbuminuria and KIM-1 for showing their effects on renal progression.

Materials and methods

Study design and participants

This prospective case-control study was performed in the Pediatric Nephrology outpatient clinic between March 2011 and February 2012. Before the study, approval was obtained from the local ethics committee of Bakırköy Dr.Sadi Konuk Training and Research Hospital on 23 May 2011 with the number 2011/06-09. Written informed consent forms were obtained from the patient, and the patient's mother and/or father, after thorough information was given about the aim and scope of the study, which was in line with principles of the Helsinki Declaration. The number of children to be included in each group was calculated with a confidence interval of 95% and a power of 90% by the G-Power 3.1 program. Thirty-eight patients and 39 healthy, age-matching controls were enrolled. The patient group included 25 females and 13 males, whereas the control group consisted of 25 females and 14 males. The patients were randomly selected from those who were referred to the Pediatric Nephrology outpatient clinic with incidentally detected microscopic hematuria. The inclusion criteria were an absence of renal pathology and being followed up with IMH for at least four years. The patients with urinary tract infections, urinary tract stones, those with congenital anomalies of the urinary system Alport Syndrome, IgA nephropathy, nutcracker syndrome, a history of Henoch-Schoenlein Purpura, hypertension, proteinuria, or glomerulonephritis were excluded from the study.

Laboratory studies

After detailed medical history was obtained, urine culture, a full urine analysis, spot urine biochemistry, hemogram, erythrocyte sedimentation rate (ESR) and biochemical analysis of the blood, parathormone, ferritin, complement 3 (C3), C-reactive protein (CRP), anti-streptolysin O (ASO) tests, throat culture analyses as well as renal ultrasound scans were performed, and reports were reviewed and recorded. First and mid-stream urine samples were obtained to evaluate the association of KIM-1 levels with IMH. The urine sample collected was centrifuged at 4,000 rpm for 10 minutes and the supernatant was transferred into the tubes and stored at (-80°C) until analysis. After collection of all samples, KIM-1 levels were measured by quantitative sandwich enzyme immunoassay technique through human urinary TIM-1/KIM-1/HAVCR Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA). The results were recorded in ng/dL. Creatinine levels were also analyzed in the same urine sample. KIM-1 was proportioned to creatinine and expressed in ng/mg creatinine.

Statistical analysis

SPSS 23.0 package program was used for the statistical analysis of the data. Along with descriptive statistical methods (mean, standard deviation, median, interquartile range), the Mann-Whitney-U test was used to compare binary groups, the independent t-test was used to compare binary groups with normal distribution, and the chi-square test was used for the comparison of qualitative data. The area under the ROC curve was calculated for different cut-offs for KIM-1, and the sensitivity, specificity, positive predictive value, cut-off, and LR (+) values were found. The results were evaluated at 95% confidence interval and a significance level of $P<0.05$.

Results

There were no participants with a history of familial hematuria among both the control and the study groups. Similarly, the families of the participants did not have any chronic renal disease, or deafness and loss of vision, which may be associated with Alport Syndrome. Ultrasound findings of the urinary system were normal in all cases. Demographic data and blood pressure levels of the cases enrolled in the study were presented in Table 1. There were no significant differences between the two groups in terms of gender distribution, mean age, height, and body weights ($P=0.877$, $P=0.880$, $P=0.227$ and $P=0.152$, respectively). Their mean systolic and diastolic blood pressures were also similar ($P=0.147$ and $P=0.345$, respectively).

Table 1: Demographic data and clinical characteristics of the patient and control groups

Parameters		Patients (n=38)	Controls (n=39)	*P*-value
Gender	Male n (%)	13 (34.21)	14 (35.90)	0.877
	Female n (%)	25 (65.79)	25 (64.10)	
Parameters		Mean (SD)	Mean (SD)	*P*-value
Age (years)		8.47 (3.46)	8.36 (3.18)	0.880
Height (cm)		124.69 (31.44)	131.59 (16.11)	0.227
Body weight (kg)		37.06 (26.06)	30.54 (10.53)	0.152
SBP (mmHg)		100.66 (11.52)	104.74 (12.87)	0.147
DBP (mmHg)		60.92 (8.29)	59.36 (5.98)	0.345

SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

The blood tests performed to exclude the causes of hematuria in the patients were presented in Table 2. Blood hemoglobin levels were significantly lower in the patient group when compared with the control group (P=0.049). However, the two groups were similar with regards to leukocyte and platelet count, prothrombin time, activated partial thromboplastin time, urea, and C3 levels (P>0.05). CRP levels were significantly higher in the patient group than the control group (P=0.028); while ESR, uric acid, creatinine, calcium, ASO, parathormone, and ferritin levels were similar (P>0.05).

This study mainly focused on the urine analysis findings, which were shown in Table 3. While the mean urine pH, calcium, uric acid, magnesium levels, creatinine, uric acid to creatinine, and magnesium to creatinine rates in spot urine were similar between the two groups (P=0.214, P=0.818, P=0.804, P=0.307, P=0.051, P=0.203, and P=0.945, respectively), the mean urine density, erythrocyte count, spot urine microalbumin level, microalbumin to creatinine rate, KIM-1 level, and KIM-1 to urine creatinine ratio of the study group were significantly higher compared to those of the control group (P=0.003, P=0.001, P=0.016, P=0.013, P=0.001, and P=0.001, respectively).

Table 2: Comparison of blood analysis findings in the patient and control groups

Parameters	Patients (n=38) Mean (SD)	Controls (n=39) Mean (SD)	*P*-value
Hemoglobin (gr/dL)	12.03 (0.75)	12.39 (0.85)	0.049
Leukocyte (mm^3)	7.91 (2.49)	8.45 (3.5)	0.438
Platelets (mm^3)	282.89 (75.15)	315.03 (91.87)	0.098
Prothrombin time (sec)	12.67 (3.28)	11.9 (0.84)	0.164
aPTT (sec)	33.56 (11.2)	31.91 (6.88)	0.438
Complement 3 (mg/dL)	128.93 (23.12)	129.09 (24.64)	0.978
Parameters	Median (min-max)	Median (min-max)	*P*-value
Uric acid (mg/dL)	3.3 (2.18-4.05)	3.4 (2.7-3.8)	0.748
Creatinine (mg/dL)	0.5 (0.43-0.54)	0.5 (0.4-0.5)	0.347
Calcium (mg/dL)	4.25 (2.3-9)	6.2 (2.3-10.3)	0.727
ESR (mm/h)	16 (4.25-28)	12 (2-18)	0.247
ASO (U/mL)	182.4 (37.73-299.58)	140 (45.1-212.8)	0.173
CRP (mg/dL)	0.14 (0.06-0.76)	0.05 (0.03-0.25)	0.028
PTH (pg/mL)	25.2 (17.33-42.4)	29.3 (20.8-41.8)	0.386
Ferritin (ng/mL)	30.1 (21.31-47.55)	26.9 (14.06-36.37)	0.137

SD: Standard deviation, aPTT: Activated partial thromboplastin time, ESR: Erythrocyte sedimentation rate, ASO: Anti-streptolysin O, CRP: C-reactive protein, PTH: Parathyroid hormone

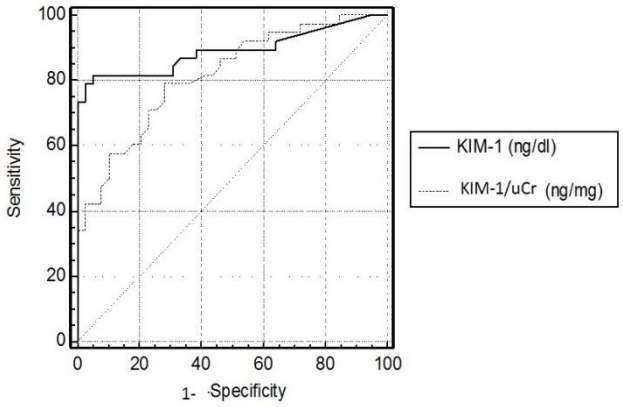
Table 3: Comparison of urine microscopy and biochemical findings between the patients and controls

Parameters	Patients (n=38) Mean (SD)	Controls (n=39) Mean (SD)	*P*-value
pH	5.71 (0.65)	5.92 (0.85)	0.214
Density	1019.32 (5.91)	1014.67 (7.08)	0.003
Erythrocyte/per area (count)	134.68 (55.79)	1.77 (1.27)	0.001
Parameters (In spot urine)	Median (min-max)	Median (min-max)	*P*-value
uCr (mg/dL)	73.53 (13.4-156.00)	89.35 (21.20-184.00)	0.113
uCa (mg/dL)	7.21 (2.30-15.00)	7.39 (2.80-18.00)	0.818
uCa/uCr (mg/mg Cr)	0.15 (0.02-0.47)	0.10 (0.03-0.25)	0.051
uUA (mg/dL)	50.02 (24.00-85.00)	50.87 (24.00-85.00)	0.804
uUA/uCr (mg/g Cr)	1.07 (0.15-3.97)	0.82 (0.22-3.30)	0.203
uMA (mg/dL)	10.74 (2.00-36.90)	6.92 (2.10-14.00)	0.016
uMA/uCr (mg/mg Cr)	0.19 (0.02-0.81)	0.10 (0.02-0.49)	0.013
uKIM-1 (ng/dL)	165 (106.5-201.8)	36 (15-72)	0.001
uKIM-1/uCr (ng/mg Cr)	1.47 (0.89-2.61)	0.59 (0.32-1.0)	0.001

SD: Standard deviation, Ca: Calcium, Cr: Creatinine, UA: Uric acid, MA: Microalbumin, uKIM-1: Urinary kidney injury molecule-1

The ROC analyses of urine KIM-1 and KIM-1 to uCr were reviewed for the differential diagnosis of hematuria. The area under the curve was 0.891 (0.035) for KIM-1 with a cut-off of >92%, a sensitivity of 81.58%, a specificity of 94.87%, a positive predictive value of 93.9%, a negative predictive value of 84.1%, and a positive likelihood ratio (LR+) of 15.91. These results revealed that hematuria probability in a patient with KIM-1 >92% was 15.91-fold of that of a patient with KIM-1 <92%. The area under the curve was 0.815 (0.049) for KIM-1/uCr, with a cut-off of >80%, a sensitivity of 78.95%, a specificity of 71.79%, a positive predictive value of 73.2%, a negative predictive value of 77.8%, and an LR+ value of 2.80. The hematuria probability in a patient with KIM-1 >80 was 2.80-fold of that of a patient with KIM-1 <80% (Figure 1).

Figure 1: Importance of urinary KIM-1 and urinary KIM-1 to urine creatinine ratio for identification of hematuria



Discussion

We found that uKIM-1 and microalbumin levels in the spot urine as well as these parameters to uCr ratio are higher in children with IMH compared to the control group. However, the elevation in uKIM-1 was more significant than the uMA. As it is non-invasive, we think that performing this test should be considered for IMH monitoring in children.

Although pediatric IMH is mostly associated with benign causes, it may rarely cause chronic kidney damage [5, 8, 11]. We did not perform a renal biopsy on our patients, because it is not the right approach. Renal biopsy is not recommended if there is no suspicion of IgA nephropathy, Alport syndrome, familial thin basement membrane disease, and other glomerulopathies. Demographic data, physical examination findings, blood pressure levels, and laboratory findings of the patients and controls enrolled in the study were normal in both groups and did not significantly differ. Renal function tests were within normal limits. These findings suggest that our patients were unlikely to have any disease other than IMH. However, lower hemoglobin and higher CRP levels in the patient group may be indicative of mild chronic inflammation.

Analysis of spot urine findings of the patient and control groups revealed that urine density and erythrocyte count per area under the microscope were significantly higher in the patient group than in the control group. The lack of significant difference in terms of calcium, creatinine, uric acid, magnesium levels in spot urine shows the absence of various etiological causes of hematuria, including hypercalciuria and hyperuricosuria in our patients. Similarly, there were no significant differences in serum ESH, ASO, parathormone, ferritin, urea, uric acid, creatinine, C3, calcium, phosphor, and alkaline phosphate levels. All these results support the diagnosis

of IMH in our patients. Higher KIM-1 levels, as well as KIM-1 to Cr ratio, indicate that these patients are in the risk group for the progression to chronic kidney diseases. Although serum Cr and cystatin C levels are mainly used to determine this risk, they are increased later than the new biological markers. There are numerous studies conducted on the KIM-1 biomarker in the literature. Significantly higher levels of urine KIM-1 from the first day of AKI diagnosis guide us for the diagnosis and treatment of AKI [12-14, 21-23]. A study conducted on 249 patients diagnosed with AKI detected elevated levels of NGAL, KIM-1, and IL-8 on the first day of diagnosis [24]. Matrix metalloproteinase 3, serum albumin, and TNF have regulatory roles in the release of KIM-1 from proximal tubular epithelial cells [25], and the early elevation in KIM-1, cystatin C, IL-8, and L-FABP levels and dialysis need decrease with early diagnosis [26]. These findings show the necessity of advanced examinations before renal biopsy for assessing the underlying renal pathology in IMH patients with higher urine KIM-1 levels. Children with IMH should be monitored for renal progression.

Higher urine microalbumin, as well as microalbumin to creatinine ratio, support the idea that these patients are in the risk group for the progression of chronic kidney disease. Although serum creatinine and cystatin C levels are mostly used to determine this risk, they increase later than the new biological markers. The effects of microalbuminuria and proteinuria on renal progression are well known [27]. Microalbumin to Cr ratio reflects renal disease progression [28]. For example, persistent MA in urine in Type 1 Diabetes Mellitus patients progresses to end-stage renal disease [29]. Higher MA and KIM-1 levels, and their ratio to creatinine in IMH patients are crucial findings in our study. The elevation in KIM-1 was more significant than that in MA, which shows that IMH patients should be monitored for renal tubular injury and the development of chronic renal disease. The relationship of these two markers with each other should also be emphasized.

Limitations

One of the limitations of the present study was the small number of patients. We also could not exclude IgA nephropathy, thin basal membrane disease, and Alport syndrome which are important in the etiology of microscopic hematuria and may only be diagnosed with renal biopsy even medical history and laboratory findings do not match. Therefore, comprehensive studies with more extensive case series should be performed for the association of hematuria and KIM-1.

Conclusion

KIM-1, KIM-1/uCr, MA, and MA/uCr can be used to monitor disease progression in IMH. Along with urine microalbumin, the elevation of KIM-1 suggests the necessity of further analysis when hematuria is detected, and it is a non-invasive test that may be used conveniently during follow-up. Slightly higher CRP levels of these patients indicate a persistent inflammation. Blood hemoglobin levels were negatively affected by persistent microscopic hematuria and chronic inflammation. Therefore, patients diagnosed with IMH should be monitored regularly. In this regard, we believe that the problems will be solved better with large series in children with hematuria who underwent renal biopsy.

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Incidence and risk factors of nephrotoxicity associated with intravenous colistin use in the intensive care unit

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Ethics Committee Approval
Ethics committee approval for this study was received from the Ethics Committee of Inonu University following the Declaration of Helsinki (date: 24.07.2019; no: 2019/138).
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Abstract

Background/Aim: The most serious side effect of colistin therapy is nephrotoxicity. This study aimed to investigate the incidence of nephrotoxicity (NT) due to intravenous colistin and determine the associated risk factors in critically ill patients in the intensive care unit (ICU).

Methods: This retrospective cohort study was conducted by examining the files of 100 patients who were hospitalized in the ICU and received intravenous colistin therapy. According to the RIFLE criteria, the patients were divided into two groups as those with and without nephrotoxicity. The clinical characteristics of the patients were compared between the groups and the risk factors associated with nephrotoxicity were determined by multivariate linear logistic regression analysis.

Results: The mean age, mean length of stay in the ICU, and mortality rate of 44 patients included in the study were 68±16.36 years, 77.14 (83.03) days, and 56.8%, respectively. NT developed in 22 (50%) patients during colistin therapy. In those with NT, diabetes mellitus, chronic obstructive pulmonary disease, and coronary artery disease were significantly more common (P<0.05 for all), the mean age (P<0.001), Charlson age-adjusted comorbidity index (CACI) scores, APACHE scores (P=0.010) were higher and albumin level was lower (P=0.001). High CACI scores (B=0.532, P=0.002) and low albumin levels (B=-0.323, P=0.023) were significant risk factors for colistin NT according to the regression analysis.

Conclusion: Nephrotoxicity is significantly common among critically ill patients receiving colistin therapy. Patients with high CACI scores and hypoalbuminemia should be followed up closely for nephrotoxicity.

Keywords: Colistin, Nephrotoxicity, Intensive care unit

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Introduction

Nosocomial infections due to multi-drug resistant (MDR) gram-negative bacteria are associated with mortality, morbidity, and long hospitalization, especially in the intensive care units (ICUs) [1]. Colistin (colistimethate sodium) is one of the widely used intravenous (IV) agents in the treatment of these infections [2]. Its use was suspended in the 1970s due to high rates of nephrotoxicity (NT), but it has recently regained popularity because of the increase in MDR nosocomial infections in recent years [2,3].

The most common side effects that limit the use of colistin are nephrotoxicity and neurotoxicity. Both are dose-dependent and reversible, and permanent kidney damage is rarely seen. The rate of colistin-related nephrotoxicity varies between 20-76% in numerous studies [2, 4, 6]. Although the underlying mechanism is not clear, it was reported to cause an increase in membrane permeability and oxidative damage, resulting in acute tubular necrosis [6, 7].

Factors affecting the risk of nephrotoxicity include age, gender, hypoalbuminemia and hyperbilirubinemia, high-dose and long-term use of colistin, use of additional nephrotoxic agents, and various comorbidities [6]. Colistin nephrotoxicity is associated with increased adverse outcomes in critically ill patients [1]. For this reason, determining the risk factors associated with nephrotoxicity is critical in preventing nosocomial infections with MDR in the ICU.

This study aims to investigate the frequency of nephrotoxicity due to IV colistin use in the intensive care unit and determine the associated risk factors.

Materials and methods

Study design and environment

This retrospective observational study was conducted by examining the files of patients hospitalized in a tertiary ICU between May 2018-May 2019. Adult patients who received at least 48 hours of IV colistin therapy were included in this study; while patients followed in the cardiovascular surgery ICU, those with acute or chronic renal failure, those who received hemodialysis, patients under 18 years of age, and pregnant women were excluded. In patients who received colistin therapy more than once, their first use was assessed (Figure 1). This study was performed per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.

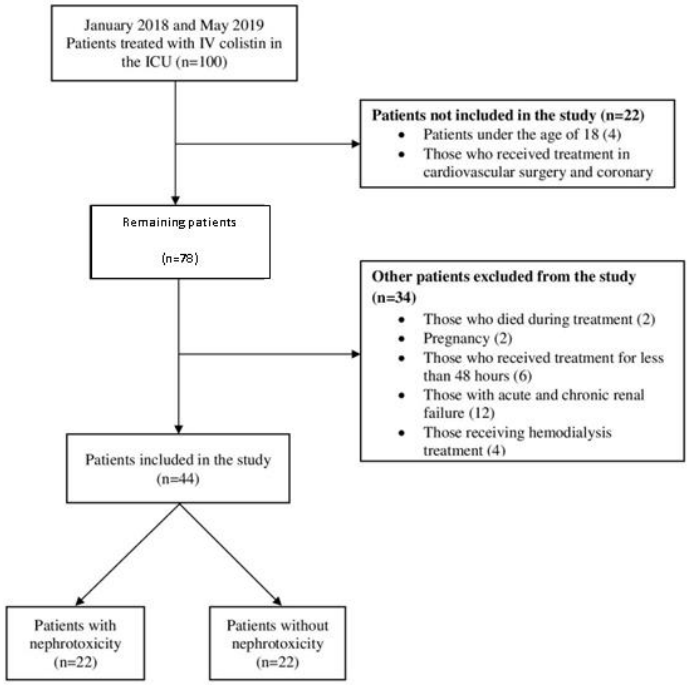
Study data

All included patients were in critical condition and received IV colistin due to gram-negative infections with MDR in the ICU. The data were obtained by scanning the hospital information management system, patient files, and daily ICU follow-up forms. Demographic characteristics of the patients, length of stay in the ICU, comorbid diseases, Charlson age-adjusted comorbidity index (CACI) scores, infection location and causative microorganisms, Acute Physiology and Chronic Health Evaluation (APACHE) II scores at diagnosis and albumin values were recorded. After at least 48 hours of IV colistin therapy, the amount of colistin received, the number of days until nephrotoxicity developed, and mechanical ventilation (MV), hemodialysis requirements, and inotropic agent needs were noted.

RIFLE criteria were used for the evaluation of nephrotoxicity. The patients were divided into two groups as those with and without NT. In cases of nephrotoxicity, nephrology and infectious diseases departments were informed. Recommendations for change in IV the colistin treatment regimen or dose adjustment were followed. Comorbidities of the patients were confirmed by preoperative consultation records. The CACI scores of the patients were calculated on the website http://www.pmidcalc.org/id=7722560&newtest=Y' and their results were noted [8].

Nosocomial infection diagnoses were made according to the “Centers for Disease Control and Prevention” criteria in daily visits performed in the ICU by the infectious diseases department. The analyzed infection-related data were obtained from patient files, the hospital automation system, and the database of the National Hospital Infections Surveillance Network. The use of other nephrotoxic agents (aminoglycoside, carbapenem, vancomycin, tigecycline, sulbactam, contrast agent, etc.) used in combination with colistin was recorded and compared between the groups.

Figure 1: Flow chart of the study



Ethical statement

Ethics committee approval for this study was received from the Ethics Committee of the Inonu University following the Declaration of Helsinki (date: 24.07.2019; no: 2019/138).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 package program. The data were presented as number (%), median and interquartile range (25-75 p). The suitability of the variables to normal distribution was evaluated with the Kolmogorov–Smirnov test. Non-normally distributed continuous variables were compared with the Mann-Whitney U test. Categorical variables were compared using Pearson's Chi-square test and Fisher's exact test, as needed. Risk factors affecting the RIFLE scores were found by the enter method in multivariate

sequential logistic regression analysis. $P<0.05$ was considered statistically significant.

Sample size calculation was based on the study of Kaya et al. [16] on the incidence of colistin-related nephrotoxicity. A total of 40 patients were required for one-sided, 0.05 error and 85% power. Sample size estimation was made using G*Power (version 3.1.9.6; Kiel, Germany) software.

Results

Demographic data and clinical characteristics of the patients

The data of 44 patients who met the inclusion criteria among 100 patients who received IV colistin therapy due to nosocomial infection in the ICU were analyzed retrospectively (Figure 1). Nephrotoxicity developed in 22 (50%) patients (with NT) during colistin therapy, while it was not observed in 22 (50%) (without NT). Twenty-seven (61.4%) patients were male, 17 (38.6%) were female, and the overall mean age was 68 (16.36) (range: 20-92) years. The mean length of stay in ICU was 77.14 (83.03) (range: 10-356) days, and 25 (56.8%) patients died. The demographic characteristics of the patients are presented in detail in Table 1.

Table 1: Comparison of demographic characteristics and prognosis in patients with and without nephrotoxicity

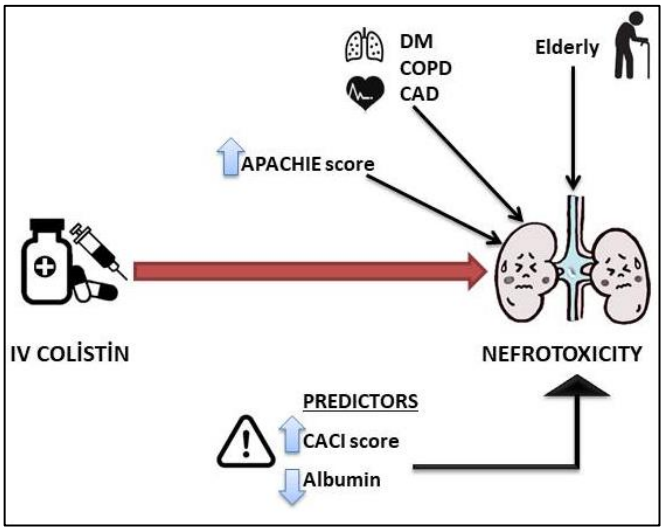
Patient characteristics		Patient without NT (n=22)		Patient with NT (n=22)		All patients (n=44)		*P*-value
Gender	Male	13	59.1%	14	63.6%	27	61.4%	0.757*
	Female	9	40.9%	8	36.4%	17	38.6%	
Age (years)		64	55-70	79	68-84	69	62-80	<0.001‡
Site of infection	Respiratory	13	59.1%	8	36.4%	21	47.7%	0.183†
	Blood circulation	4	18.2%	8	36.4%	12	27.3%	
	Urinary tract	4	18.2%	2	9.1%	6	13.6%	
	Other	1	4.5%	4	18.2%	5	11.4%	
Infectious agent	Acinetobacter	14	63.6%	9	40.9%	23	52.3%	0.406†
	Klebsiella	4	18.2%	7	31.8%	11	25.0%	
	Pseudomonas	3	13.6%	3	13.6%	6	13.6%	
	Others	1	4.5%	3	13.6%	4	9.1%	
Comorbidities	Diabetes mellitus	4	18.2%	11	50.0%	15	34.1%	0.026*
	Hypertension	13	59.1%	18	81.8%	31	70.5%	0.099*
	Neurologic disease	9	40.9%	4	18.2%	13	29.5%	0.498*
	Chronic obstructive pulmonary disease	15	68.2%	17	77.3%	32	72.7%	0.030*
	Cancer	7	31.8%	5	22.7%	12	27.3%	0.698*
	Liver failure	17	77.3%	10	45.5%	27	61.4%	0.664*
	Coronary artery disease	5	22.7%	12	54.5%	17	38.6%	0.026*
Mortality		11	50.0%	14	63.6%	25	56.8%	0.361*
Renal replacement therapy		6	27.3%	13	59.1%	19	43.2%	0.033*
Need for MV		13	59.1%	21	95.5%	34	77.3%	0.045*
Need for inotropic support		13	59.1%	18	81.8%	31	70.5%	0.099*
Length of stay (days)		45	28-100	34	24-96	40	26-98	0.664‡
CACI score		3	2-4	5	4-6	4	3-5	<0.001‡
APACHE score		22	12-24	25	22-36	24	18-26	0.010‡
Duration of treatment, days		8.5	5.75-14	7.5	5-9.25	8	5-10.75	0.062‡
Duration of colistin treatment, days		5.5	4-8	4.5	3-6	5	4-6	0.089‡
Albumin level (g/dl)		2.80	2.55-3.40	2.20	1.90-2.65	2.58	2.15-2.95	0.001‡
Use of additional nephrotoxic agents		19	%86.4	20	%90.4	39	%88.6	0.635*

*Chi-square test; †Fisher exact test; ‡ Mann Whitney U Test, It was presented as n (%) and median (25-75 p.). MV: Mechanic ventilation; CACI: Charlson Age-Adjusted Comorbidity Index

Comparison of clinical characteristics between nephrotoxicity groups

The mean age was significantly higher in the group with NT compared to the group without (77.09 (9.6) vs 58.9 (16.8)) ($P<0.001$), but gender distribution was similar ($P= 0.757$) (Table 1). While diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD) were significantly more common in the group with NT ($P=0.026$, $P=0.030$, and $P=0.026$, respectively), there were no significant differences in terms of other comorbidities (each $P>0.05$). In addition, CACI scores were significantly higher in the NT group ($P<0.001$) (Figure 2).

Figure 2: Risk factors associated with nephrotoxicity



The foci of infection in order of frequency were the respiratory tract (47.7%), blood circulation (27.3%), and the urinary tract (13.6%). The most common infectious agents were Acinetobacter (52.3%), Klebsiella (25.0%), and Pseudomonas spp. (13.6%). These results did not differ between the two groups.

Data

Total treatment time of colistin and days until NT development did not differ between the groups. While the hospitalization period was insignificantly shorter, and mortality was insignificantly higher, MV support, hemodialysis need, and APACHE scores were significantly higher, and mean serum albumin level was significantly lower in the group with NT ($P=0.045$, $P=0.033$, $P=0.010$, and $P=0.001$, respectively). The two groups were similar in terms of inotropic agent need ($P>0.05$). Five patients (11.4%) received colistin monotherapy and 39 (88.6%) received combination therapy with other nephrotoxic agents. The rate of those who received additional nephrotoxic agents did not differ between the groups ($P=0.365$).

Independent risk factors for nephrotoxicity

According to the RIFLE scoring system, half (50%) of the patients had no renal damage, 9.1% carried a risk, 15.9% had damage and 25% had renal insufficiency (Table 2). Risk factors affecting RIFLE scores were determined by multivariate logistic regression analysis: High CACI scores (*B:* 0.532, $P=0.002$) and low albumin levels (*B:* -0.323, $P=0.023$) were significant risk factors for colistin nephrotoxicity (Table 3).

Table 2: Nephrotoxicity rates by RIFLE classification

RIFLE criteria	n	%
No	22	50.0%
Risk	4	9.1%
Damage	7	15.9%
Failure	11	25.0%

Table 3: Multivariate ordinal logistic regression analysis of possible factors affecting the RIFLE classification

$R^2=0.510$	ß	SE	Beta	t	*P*-value
Constant	0.891	1.296	-	0.687	<0,001
Age	0.009	0.015	0.109	0.561	0.578
CACI	0.398	0.118	0.537	3.363	0.002
APACHE-II	0.032	0.020	0.201	1.610	0.116
Albumin	-0.605	0.255	-0.323	-2.374	0.023

SE: Standard error; CACI: Charlson age comorbidity index; APACHE: Acute Physiology and Chronic Health Evaluation

Discussion

Colistin-related nephrotoxicity rates vary between 20% and 76% in different studies [5]. This difference may be due to different scoring systems (AKIN, RIFLE, and KDIGO) used for renal failure [9]. In the present study, RIFLE criteria were used to determine the risk of colistin-related nephrotoxicity, as suggested by various studies [1, 7, 12]. Our rate of NT was higher (50% of the patients), which may be because our patient population consists of critically ill patients of advanced age and the right treatment dose of colistin could not be adjusted.

Many factors, including advanced age, male gender, comorbidities (DM, HT, etc.), obesity, hypoalbuminemia, hyperbilirubinemia, nephrotoxic drug use, total colistin dose and duration, and contrast agent administration, are found to increase the risk of colistin-related nephrotoxicity [6, 10-12]. Extensive studies report that advanced age and chronic multiple comorbid diseases are important risk factors for drug-related kidney injury [6, 10, 11]. Conversely, studies are reporting that advanced age does not play a role in NT [12]. In a study investigating the relationship of colistin NT with age, NT was associated with being over 60 years of age and high CACI scores [10]. In our study, the mean age of patients with NT was higher, and DM, COPD, and CAD were more common. CACI index is a widely used clinical scoring system that evaluates the patient's physical condition and age and determines the prognosis depending on the patient's comorbidities [8]. Various studies report that the CACI score is associated with acute kidney injury in critically ill patients [6, 8]. Similarly, in our study, the CACI score was an independent risk factor for colistin-associated NT. However, CACI is not yet fully considered an independent risk factor for colistin-associated NT due to insufficient data.

In numerous studies, the most common site of infection is the respiratory tract, and the infectious agents are Acinetobacter, Klebsiella, and Pseudomonas spp. [1, 13-15], like our findings. The relationship between colistin dose, duration of use and NT are still contradictory [6, 14, 16]. There are studies reporting that the duration and amount of colistin affect NT [13, 17]. Colistin-associated NT usually occurs within the first 5 days of treatment and may be reversible after the treatment is terminated [18]. Jason et al. [16] state that NT developed within the first 7 days in 78% of the patients, Emrah et al. [1] reported that it developed within the first 9 days in 77%, and in the study of Deryke et al. [17], NT developed in the first 5 days in all patients. On the other hand, we found no significant relationship between the duration of colistin use and NT.

Another risk factor associated with NT is the combinational use of nephrotoxic agents with colistin. Despite conflicting reports, the use of additional nephrotoxic agents was associated with kidney damage in most studies [14]. There are also studies reporting that it does not affect NT [10, 11, 13, 16, 17]. Kim et al. [14] stated that the combined use of various NT agents (NSAID, aminoglycoside and diuretic, etc.) is a risk factor for colistin NT. In our study, the combined use of colistin with nephrotoxic agents did not significantly affect NT. However, caution should be exercised in the use of additional nephrotoxic agents (contrast agent, NSAID or aminoglycoside, etc.).

Hypoalbuminemia was the second independent risk factor for NT in our study. The relationship between hypoalbuminemia and NT was demonstrated in many studies [14, 19, 20]. However, there is wide heterogeneity in the literature on this subject as well. In the case of hypoalbuminemia, NT may develop due to reduced binding of colistin to albumin; however, the underlying mechanism is not yet clear. Daniele et al. [19] reported that severe hypoalbuminemia (<2.5 g/dl) at the beginning of colistin therapy was a predictor of nephrotoxicity. In another study, hypoalbuminemia with a cut-off value of 2.65 g/dL was a significant predictor for NT [20]. On the other hand, various studies have shown that albumin level does not affect NT [11, 14]. Another important result in the present study is that the APACHE score, which is an indicator of mortality in critically ill patients, was significantly higher in patients with NT. Similarly, Emrah et al. [1] found that a high APACHE score was associated with colistin NT.

Although colistin nephrotoxicity is reversible, studies are reporting increased mortality [2, 6] and inotropic need, and prolonged hospitalization [1, 13, 20, 21]. We observed that patients with NT insignificantly more frequently needed inotropes, MV, and hemodialysis. Despite these negative results, there was no significant difference in mortality between the NT groups. Conversely, other studies found that colistin-associated NT is associated with high mortality [11]. Based on our results, it can be said that colistin-associated NT disrupts the clinic of critically ill patients but is not an important risk factor for mortality.

The limitations of our study include the small sample size, and its retrospective and single-center nature.

Conclusion

Our results show that nephrotoxicity during colistin therapy is common in critical patients in the ICU. Higher rates of nephrotoxicity were observed in patients with DM, COPD, and CAD. High CACI score and hypoalbuminemia were independent risk factors for colistin-associated nephrotoxicity. During colistin therapy, critical patients with these adverse risk factors should be closely monitored in terms of nephrotoxicity.

Acknowledgment

Figure 2 is original, copyrighted by the authors of this study, and was produced for this article.

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Parental anxiety during dental procedures in children under deep sedation: Anxiolysis with lavender oil and orange peel oil aromatherapies

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Ethics Committee Approval
Ankara University, Clinical Research Ethics Committee, 02/08/2019 and 09/05.
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Conflict of Interest
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Abstract

Background/Aim: Deep sedation, used for dental treatment of uncooperative pediatric patients, create added anxiety in parents. It is important to reduce the anxiety of the parents for them to understand the post-procedure instructions and overcome the problems that may arise during their implementation, which will affect the recovery process. This study investigates the anxiolytic effects of lavender oil and orange-peel oil aromatherapies on the parents of pediatric patients undergoing dental procedures with deep sedation.

Methods: This randomized controlled study includes 90 parents who were randomly divided into three equal groups: Lavender oil (Group L), orange peel oil (Group O), and control groups (Group C). Group L inhaled the diffusion of 0.3 ml lavender oil in 120 ml water, Group O inhaled the diffusion of 0.3 ml of orange peel oil in 120 ml water, and Group C inhaled the diffusion of 120 ml of water. Parents completed the State-Trait Anxiety Index before the children were taken to the treatment room (STAI-1 and STAI-2) and after 1 hour of inhalation (STAI-1A).

Results: All three groups involved parents with similar demographic data. Parents in Group L who had children over the age of 5 years had higher anxiety scores after 1 hour of waiting (P=0.044). Also, the STAI-1 scores of unemployed parents in Group C were higher (P=0.021). In Group O, STAI-1A scores were higher than STAI-2 scores (P=0.038). The changes in STAI-1 and STAI-1A scores were similar between the groups (P=0.074).

Conclusion: Although no anxiolytic effect was observed, these methods were still considered promising. New research can be conducted with different settings and application regimes.

Keywords: Parents, Anxiety, Aromatherapy, Lavandula, Citrus sinensis

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Introduction

Anxiety is associated with pronounced psychological distress and can range from a minor ailment to extreme distress. Conscious/deep sedation is used as an alternative when nonpharmacological methods fail and routine dental treatments of children with intense anxiety cannot be performed [1]. Nevertheless, the induction of conscious/deep sedation causes additional anxiety about the procedure and carries the risk of not being able to regain consciousness. It is a stressful event often causing anxiety in the parents and may have harmful consequences for the intricately linked physiological and mental conditions of the child [2-4]. Also, this state of restless anxiousness of the parents may cause an inability to understand preoperative and postoperative instructions, which could prolong recovery time [4].

The physiological and psychological effects of essential oils have long been known in traditional medicine and aromatherapy. Lavender oil and orange oil fragrances are still popular and commonly found in households. The lavender plant belongs to the Labiatae family and has been used in dried form or as an essential oil for centuries. It is usually obtained from the flower head and leaves by steam distillation method [5]. The orange plant belongs to the family Rutaceae. Orange oil is obtained from fruit peels by cold pressing or distillation [6]. These oils are believed to have antibacterial, antifungal, muscle relaxant, sedative, antidepressant, and mood-lifting effects in traditional medicine and are beneficial for burns and insect bites [5, 6]. Essential oils have also been investigated for their anxiolytic features [7]. However, during the literature search, no study could be found investigating the anxiolytic effects of these oils on parental anxiety during the dental treatment of a child under sedation.

The purpose of the present study was to investigate the possible anxiolytic effects of lavender oil and orange-peel oil on parents of pediatric patients undergoing deep sedation.

Materials and methods

The Institutional Ethics Review Board of Ankara University Faculty of Dentistry approved this study (No. 09/05 ClinicalTrials.gov identifier NCT04079309), and the medical protocol of the study followed the Declaration of Helsinki.

This 3-armed randomized controlled trial was conducted at Ankara University, Faculty of Dentistry, Department of Pedodontics (Ankara, Turkey), with the informed consent of the participants. The inclusion criteria were being >18 years, able and willing to complete anxiety tests, and parents to children with indications for dental treatment under deep sedation according to the Frankl behavior assessment scale [8] (children with intense anxiety and cooperation problems and who could not be treated with the psychological approach methods). Parents with hypersensitivity to lavender and orange products, any psychiatric or psychological problems, those using any kind of medications, or those who did not agree to participate were excluded. As procedure times can vary, the procedural time for the pediatric interventions was 1 hour, and cases with a procedural time <1 hour were excluded from the study.

The study involved 96 parents, divided into three groups (Group L-lavender oil (n=30), Group O-orange peel oil (n=30), and Group C-control group (n=30)) using block randomization with a computer-generated program. The demographic data included age, gender, educational and occupational status of the parents and age, and concomitant diseases of the child.

To measure the state and trait anxiety scores of the parents, the Turkish State-Trait Anxiety Inventory (STAI-1 and STAI-2), which is effective in diagnosis and counseling in Turkey, was used. STAI-1 (evaluating trait anxiety) and -2 (evaluating state anxiety) were administered to the parents before the children were taken to the treatment room [9]. An essential oil vaporizer (TaoTronics) was placed in the 6 m^2 waiting room and activated 30 min before the participants entered. Lavender oil (*Lavandula angustifolia* Miller; Herba-flora, Ankara, Turkey), 0.3 ml diffused in 120 ml of water, orange peel oil (*Citrus sinensis*; Balen, Ankara, Turkey), 0.3 ml diffused in 120 ml of water, and 120 ml of water were placed in the essential oil vaporizer for Groups L, O, and C, respectively. The participants inhaled the room air with the essential oil vapors for 1 hour. The parents entered a waiting room once the children were taken into the treatment room. The second STAI-1 was readministered after 1 hour of a wait as STAI-1A. The parents completed the questionnaires at their own pace. They were not informed about the lavender or orange scents, as this may have affected the questionnaire results before completing the survey. However, all participants were informed about the study, and informed consent was obtained to use the data after completing the study.

Statistical analysis

Based on the results of previous studies, under the assumption that the mean (SD) values of STAI scores were 38.0 (10.2) and 42.3 (8.3), the paired t-test was used for sample calculation with a power of 0.80 at the significance level of 0.05. A minimum of 29 parents was sufficient for each arm of the study. The data analysis was completed with SPSS v11.5 software, Windows version (SPSS Inc., Chicago, IL, USA). Descriptive data were evaluated using mean (SD), and median (range), and the number of teeth (%) were used for qualitative variables. The data were not normally distributed; hence, the Mann-Whitney-U test was used to evaluate the quantitative variables and whether there was a difference between the two categories of qualitative variables. A one-way analysis of variance was used for normally distributed quantitative variables with more than two categories, and the Kruskal-Wallis H test was used for non-normally distributed quantitative variables. The Wilcoxon sign test was utilized to evaluate differences between two dependent quantitative variables. The relationship between two categorical variables was examined using the chi-square or Fisher's exact tests. Logistic regression was used to determine the risk factors affecting the qualitative variables in two dependent categories. A *P*-value <0.05 was considered significant.

Results

Six parents with a pediatric procedural time of <1 hour were excluded from the study. The final study population consisted of 90 (55 females and 35 males) parents. The CONSORT flow diagram is presented in Figure 1.

Figure 1: CONSORT flow diagram

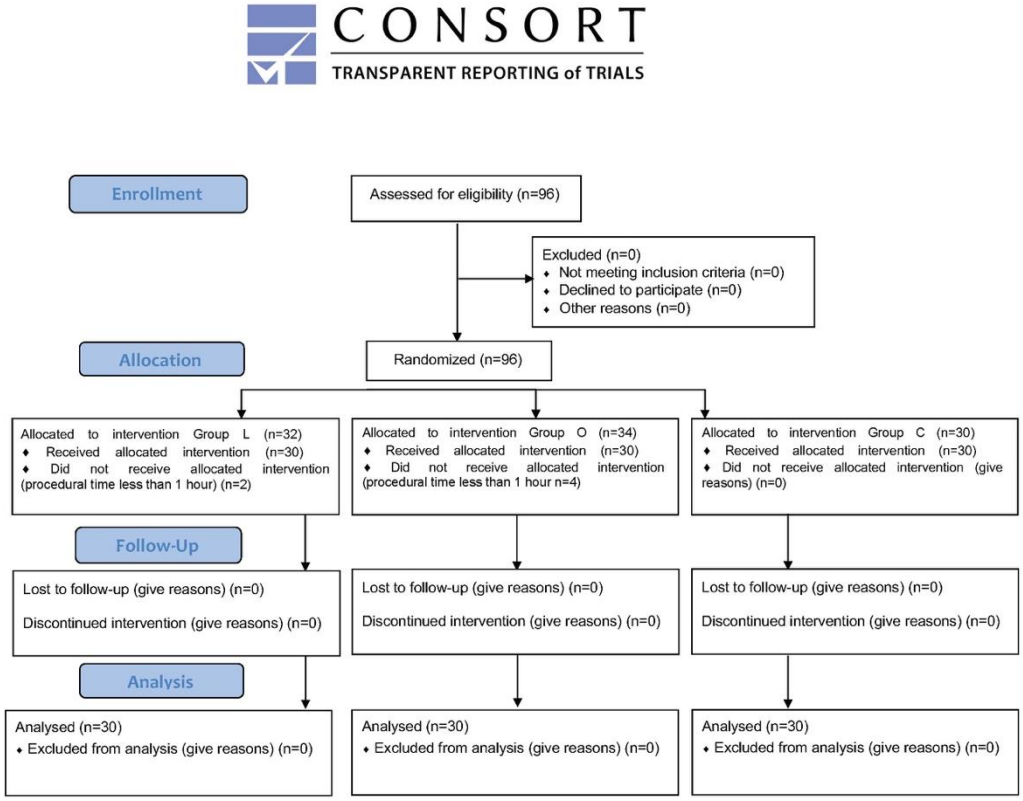

Table 1: The relationship between demographic data and distribution of STAI-1, STAI-2, and STAI-1A scores for Group L

Variables		STAI-1			STAI-2			STAI-1A		
		Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value
Age	18–40 (n=16)	44.81 (11.98)	43 (20–64)	0.252[a]	42.38 (10.83)	41.50 (22–63)	0.603[a]	40.75 (11.13)	41 (20–59)	0.803[a]
	≥ 40 (n=14)	40.21 (10.11)	41 (24–58)		40.93 (8.69)	39.50 (29–59)		40.71 (9.77)	43 (24–59)	
Gender	Female (n=16)	43.19 (11.06)	41(30–64)	0.967[a]	41.56 (9.63)	39.50 (27–63)	0.739[a]	41.63 (10.66)	42.50 (23–59)	0.588[a]
	Male (n=14)	42.07 (11.74)	43 (20–58)		41.86 (10.24)	41.50 (22–59)		39.71 (10.26)	42 (20–59)	
Educational Status	PSG (n=8)	44.13 (10.26)	41.50 (33–64)	0.664[b]	44.75 (11.13)	44 (27–63)	0.257[b]	42.38 (10.41)	42.50 (23–59)	0.856[b]
	HSG (n=11)	40.09 (9.35)	39 (24–58)		43.27 (9.05)	46 (29–59)		39.91 (10.06)	39 (28–59)	
	UG (n=11)	44.18 (13.83)	49 (20–62)		37.91 (9.01)	36 (22–56)		40.36 (11.40)	43 (20–58)	
Employment Status	Unemployed (n=10)	43.10 (9.94)	43 (30–64)	0.912[a]	43 (11.24)	44 (27–63)	0.809[a]	41.50 (11.02)	44 (23–59)	0.582[a]
	Employed (n=20)	42.45 (12.02)	39.50 (20–62)		41.05 (9.16)	39.50 (22–59)		40.35 (10.26)	42 (20–59)	
Age of the Child	< 5 (n=4)	35.25 (11)	37.50 (20–46)	0.246[a]	33 (11.34)	31 (22–48)	0.099[a]	31.75 (9.14)	34 (20–39)	0.044[a]
	≥ 5 (n=26)	43.81 (10.99)	43 (24–64)		43.04 (8.99)	41.50 (29–63)		42.11 (9.95)	43 (23–59)	
Additional Diseases of the Child	Autism (n=4)	42.50 (9.95)	44.50 (30–51)	0.309[a]	43.75 (12.15)	41.50 (33–59)	0.309[a]	46.75 (3.95)	47.50 (42–50)	0.078[a]
	Other (n=4)	36.75 (11.70)	37 (24–49)		38.75 (9.11)	39.50 (29–47)		34.75 (10.31)	35 (24–45)	

SD: standard deviation, a: Mann-Whitney U test, b: Kruskal-Wallis H test, PSG: primary school graduate, HSG: high school graduate, UG: university graduate

Table 2: Relationship between demographic data and distribution of STAI-1, STAI-2, and STAI-1A scores for Group O

Variables		STAI-1			STAI-2			STAI-1A		
		Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value
Age	18–40 (n=16)	44.56 (5.39)	46.50 (33–52)	0.452[a]	42.50 (7.71)	41.50 (30–64)	0.967[a]	44.44 (9.96)	42 (31–63)	0.532[a]
	≥ 40 (n=14)	45.57 (10.89)	48.50 (27–64)		42 (7.47)	43 (30–58)		41.64 (8.54)	42 (29–53)	
Gender	Female (n=18)	46.06 (8.10)	48 (30–64)	0.566[a]	43.28 (8.66)	42.50 (30–64)	0.471[a]	44.89 (10.27)	42.50 (29–63)	0.362[a]
	Male (n=12)	43.50 (8.65)	44.50 (27–55)		40.75 (5.21)	40 (31–48)		40.50 (7.15)	42 (29–53)	
Educational Status	PSG (n=8)	44 (7.05)	48 (33–50)	0.897[b]	41.38 (10.28)	39.50 (30–64)	0.338[b]	44 (11.33)	41 (31–63)	0.853[b]
	HSG (n=10)	46.90 (9.67)	47 (27–64)		44.60 (5.97)	44.50 (38–58)		44.10 (10.34)	43 (29–59)	
	UG (n=12)	44.17 (8.22)	46 (30–55)		40.92 (6.58)	41.50 (30–49)		41.75 (7.35)	41.50 (30–57)	
Employment Status	Unemployed (n=12)	45.67 (6.41)	48 (31–55)	0.865[a]	42.75 (10.01)	41.50 (30–64)	0.687[a]	43.67 (10.34)	41 (29–63)	10[a]
	Employed (n=18)	44.61 (9.47)	45.50 (27–64)		41.94 (5.49)	43 (31–49)		42.78 (8.78)	42.50 (29–57)	
Age of the Child	< 5 (n=10)	45.80 (7.04)	48 (31–54)	0.480[a]	43.30 (9.07)	42.50 (30–64)	0.775[a]	44.30 (7.60)	42 (37–63)	0.660[a]
	≥ 5 (n=20)	44.65 (8.98)	46.50 (27–64)		41.75 (6.74)	41.50 (30–58)		42.55 (10.14)	42 (29–59)	
Additional Diseases of the Child	Autism (n=2)	40 (14.14)	40 (30–50)	0.699[a]	47.50 (2.12)	47.50 (46–49)	0.121[a]	43 (8.49)	43 (37–49)	0.558[a]
	Other (n=5)	43.80 (11.61)	48 (27–55)		39.20 (6.34)	40 (31–47)		38.20 (11.26)	37 (29–57)	

SD: standard deviation, a: a: Mann-Whitney U test, b: Kruskal-Wallis H test, PSG: primary school graduate, HSG: high school graduate, UG: university graduate

Table 3: Relationship between demographic data and distribution of STAI-1, STAI-2, and STAI-1A scores for Group C

Variables		STAI-1			STAI-2			STAI-1A		
		Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value
Age	18–40 (n=23)	38.43 (8.55)	36 (21–57)	0.338[a]	37.78 (7.56	38 (20–54)	0.980[a]	40.13 (11.41)	39 (20–66)	0.220[a]
	≥ 40 (n=7)	42.14 (5.55)	43 (31–49)		37.43 (6.65)	40 (29–45)		35 (10.02)	33 (24–51)	
Gender	Female (n=21)	40.71 (6.61)	42 (28–50)	0.085[a]	38.95 (6.29)	39 (29–54)	0.212[a]	40.24 (9.79)	39 (20–63)	0.174[a]
	Male (n=9)	36 (10.33)	34 (21–57)		34.78 (8.83)	34 (20–49)		35.89 (14.01)	31 (20–66)	
Educational Status	PSG (n=3)	37.67 (5.51)	35 (34–44)	0.766[b]	42.67 (5.51)	40 (39–49)	0.329[b]	49.33 (15.28	46 (36–66)	0.091[b]
	HSG (n=13)	38 (8.28)	36 (21–50)		38 (8.55)	40 (20–54)		40.69 (9.14	41 (20–52)	
	UG (n=14)	40.86 (8.42)	43.50 (28–57)		36.36 (6.11)	34.50 (29–48)		35.07 (10.96	34.50 (20–63)	
Employment Status	Unemployed (n=11)	41.82 (6.69)	44 (32–50)	0.168[a]	38.55 (5.65)	39 (29–48)	0.620[a]	44.64 (8.97	45 (33–63)	0.021[a]
	Employed (n=19)	37.84 (8.53)	36 (21–57)		37.21 (8.14)	38 (20–54)		35.63 (11.15	35 (20–66)	
Age of the Child	< 5 (n=10)	36.20 (8.83)	35.50 (21–49)	0.234[a]	35.20 (7.73)	35 (20–48)	0.280[a]	41 (11.59	40.50 (20–63)	0.390[a]
	≥ 5 (n=20)	40.85 (7.34)	42.50 (28–57)		38.95 (6.86)	39 (29–54)		37.90 (10.08	36 (20–66)	
Additional Diseases of the Child	Autism (n=4)	45 (9.09)	44 (35–57)	-	34.25 (7.09)	32 (29–44)	-	33.25 (10.69	30.50 (24–48)	-

SD: standard deviation, a: Mann-Whitney U test, b: Kruskal-Wallis H test, PSG: primary school graduate, HSG: high school graduate, UG: university graduate

Table 4: Differences between STAI scores evaluating patients' state and trait anxiety according to groups

Variables	Group L (n=30)			Group O (n=30)			Group C (n=30)		
	Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value	Mean (SD)	Median (range)	*P*-value
STAI-1	42.67 (11.20)	41.50 (20–64)	0.829[a]	45.03 (8.27)	47.50 (27–64)	0.038[a]	39.30 (8.03)	39 (21–57)	0.185[a]
STAI-2	41.70 (9.75)	40.50 (22–63)		42.27 (7.47)	42 (30–64)		37.70 (7.25)	38.50 (20–54)	
STAI-1	42.67 (11.20)	41.50 (20–64)	0.085[a]	45.03 (8.27)	47.50 (27–64)	0.387[a]	39.30 (8.03)	39 (21–57)	0.900[a]
STAI-1A	40.73 (10.34)	42 (20–59)		43.13 (9.27)	42 (29–63)		38.93 (11.15)	37.50 (20–66)	
STAI-2	41.70 (9.75)	40.50 (22–63)	0.673[a]	42.27 (7.47)	42 (30–64)	0.484[a]	37.70 (7.25)	38.50 (20–54)	0.336[a]
STAI-1A	40.73 (10.34)	42 (20–59)		43.13 (9.27)	42 (29–63)		38.93 (11.15)	37.50 (20–66)	

Group L: Lavender oil group, Group O: Orange peel oil group, Group C: Control group, SD: Standard deviation, a: Wilcoxon signed-rank test

Table 5: Differences of STAI scores between groups

Variables	Group L (n=30)		Group O (n=30)		Group C (n=30)		
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	Mean (SD)	Median (range)	*P*-value
STAI-1	42.67 (11.20)	41.50 (20-64)	45.03 (8.27)	47.50 (27-64)	39.30 (8.03)	39 (21-57)	0.050[a]
STAI-2	41.70 (9.75)	40.50 (22-63)	42.27 (7.47)	42 (30-64)	37.70 (7.25)	38.50 (20-54)	0.080[a]
STAI-1A	40.73 (10.34)	42 (20-59)	43.13 (9.27)	42 (29-63)	38.93 (11.15)	37.50 (20-66)	0.274[a]
STAI-1 - STAI-2	0.97 (10.44)	0.50 (20-26)	2.77 (8.87)	2.50 (19-24)	1.60 (7.66)	1 (18-22)	0.471[a]
STAI-1 - STAI-1A	1.93 (6.41)	2 (2-17)	1.90 (9.81)	0.50 (16-26)	0.37 (11.04)	0 (32-27)	0.704[a]
STAI-2 – STAI-1A	0.97 (10.60)	1 (22-21)	0.87 (10.29)	2 (23-29)	1.23 (8.92)	0.50 (17-19)	0.655[a]

a: Kruskal Wallis H test

Parents in the intervention groups reported no sensation of odor during or after waiting periods. No adverse events associated with the use of lavender and orange-peel oils were encountered. There were no statistically significant differences concerning age, gender, educational status, and employment status of the parents, and age, or comorbidities of the children between the two groups ($P>0.05$ for all). The relationship between demographic data and the distribution of STAI-1, STAI-2, and STAI-1A scores for Groups L, O, and C are presented in Tables 1, 2, and 3, respectively. In Group L, parents with children ≥ 5 years of age had higher STAI-1A scores ($P=0.044$). In Group C, unemployed parents had higher STAI-1A scores ($P=0.021$).

The differences between the STAI-1, -2, and -1A scores among the groups are presented in Table 4. The only difference was observed in Group O between the STAI-1 and STAI-2 scores ($P=0.038$).

Differences in STAI scores between groups are presented in Table 5. No differences were found between the groups concerning STAI scores ($P>0.05$ for all).

Discussion

A planned procedure is stressful not only for the child but also for the parents. Parents whose children will undergo an operative procedure feel elevated levels of anxiety and fear before the procedure [1-4]. These unpleasant sensations arise from a mixture of the child's illness, hospitalization, fear of anesthesia, and fear of the operation itself. Increased parental anxiety also increases the level of anxiety in children [10-12]. Recognizing and preventing the anxiety of the parents before the intervention will enable the information given to the parents to be understood more accurately, affect the treatment process positively and increase treatment satisfaction [7].

The most distraught group of children to undergo interventions under general anesthesia are those who are accompanied by extremely anxious patients. This condition of anxiety is reported to reflect on the first post-intervention week, affecting the parents' ability to care for their children, therefore affecting the healing process, the parents, and children, as well as the caregivers during the consultation and informed consent processes. For this reason, significant negative effects have been reported in pediatric settings [13, 14].

Literacy is another factor reflecting the understanding of health problems by parents. Increased literacy results in increased understanding, and literate parents will be able to implement the postoperative directives more effectively [15]. Although some studies report that parents with less education

have worse healthcare outcomes, other studies report a positive correlation between a parent's higher educational background and the level of anxiety [11, 12]. In our study, anxiety level did not differ with education. Charana et al. [11] associated higher anxiety levels with younger children (<5 years old). Also, female gender and younger parents correlated with higher levels of anxiety. In our study, parental gender and age differences were not associated with different anxiety levels. While parental anxiety was not affected by a lower-aged child in Groups L and C, a conflicting result was found in Group O. Parental anxiety was higher after 1 hour in parents with children >5 years of age. In addition, unemployed parents in Group C had higher STAI scores after the 1-hour wait. These conflicting results may be explained by socio-cultural differences between nations and communities.

Pediatric dental treatment is a stressful experience for a parent. The anxiety that a parent feels when their child undergoes general anesthesia was documented in the pediatric anesthesiology literature [1-3]. Unfortunately, managing parental anxiety and fear is quite challenging because the use of pharmacological agents, such as benzodiazepines, is not appropriate in such situations [10, 11]. A high STAI score indicates a high level of anxiety and vice versa. Average scores ranged between 36–41 [9]. In the present study, both state and trait anxiety of the parents were scored at a maximum of 64 points.

Most patients reported using prayer, massage, and herbal products to eliminate such anxious stress. These methods are preferred by patients because they have fewer side effects, and no detrimental effects on health have been reported [7]. The orange peel and lavender oil used in the present study have been investigated for such purposes but were not studied in a pediatric setting in parents with children undergoing deep sedation. Therefore, this study evaluated parental anxiety and whether orange or lavender oil would decrease the stress levels.

Conflicting results are presented in the literature. One study investigated 5 minutes of lavender inhalation aromatherapy as a way to reduce preprocedural anxiety and reported that aromatherapy was ineffective, whereas another study investigating lavender and rose oil inhalation aromatherapy effects on dental anxiety among orthodontic patients reported a significant decrease in anxiety levels [16, 17]. A study conducted in a dental office setting also found that inhaling both lavender and orange reduced anxiety and improved the mood of the patients [18]. The present study only detected tendencies toward differences in the lavender and orange-peel inhalation groups compared to the control group; however, the differences were not significant for several reasons. One may be the elevated level of anxiety parents felt for their children. Another reason may be related to the application method, duration, and amount of the essential oils used. In this study, the parents were blinded to the procedures before the study. Thus, the amount of essential oil applied was limited. The study was designed so that the parents would not notice the odors during administration and would not affect the STAI results. Lower anxiety scores may be obtained with larger amounts of essential oils. The working time was kept at 1 hour to ensure standardization. Longer exposure of the parents to the essential oils also may have caused different effects on anxiety.

Limitations & Strengths

A limitation that should be noted is that a single dose of 0.3 ml was selected for both lavender and orange peel oil applications, referencing other studies that achieved significant results. Since the effects of oils can vary with dose, it is recommended to determine the appropriate dose to be administered by gas chromatography.

A notable strength of the study is that aromatherapy applications were performed blindly. Since the scent of lavender is known to have a calming effect among the public, it was thought that this practice would affect the results of STAI if it was known by the parents, as in most studies in the literature.

Conclusion

The lavender and orange oil aromatherapy methods used in the present study did not have significant anxiolytic effects on parents. Nevertheless, a non-significant reduction in parental anxiety was detected. This promises that anxiety may be reduced with different administration methods, different durations, and a higher amount of essential oils.

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Research article

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An alternative educational method: Computer-based simulation program for advanced cardiac life support education

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Ethics Committee Approval
Ethics committee approval for this study was obtained from the Ethics Committee of Gazi University (Date and number of documents: 09/02/2017 - E.20669).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Technology is gaining importance in medical education, along with distance learning and technology-enhanced learning systems. In certain conditions, such as the Covid-19 outbreak, adapting technology to our medical education is essential. Computer-based simulation is one of those technologies that can be used in medical education. We aimed to measure the contribution of computer-based simulation to students' knowledge of cardiac rhythms in the advanced cardiac life support (ACLS) curriculum, compared to the classic educational method.

Methods: Interns (6^{th}-grade medical students) were included in this observational study and divided into a study group and a control group. Both groups received a 2.5-hour-long ACLS rhythms lecture. Afterward, case studies were completed with a computer-based simulation program in the study group and with the classical didactic method in the control group. The participants took a multiple-choice test to measure the level of knowledge before (pre-test) and 4 weeks after (post-test) the training. "ACLS Simulator 2016" licensed program was used.

Results: A total number of 80 medical students were included in the study. There were 35 (43.75%) males and 45 (56.25%) females, with a mean age of 23.7 (1.1) years. The mean number of correct answers in the pre-training test was 12.6 (3.2), and similar between the two groups (P=0.131), but significantly increased to 15.7 (3.3) (P<0.001) after the training. In the post-training test, the study and the control groups answered 16.0 (3.6) and 15.5 (3.1) questions correctly, respectively (P=0.477).

Conclusion: Adapting a computer-based simulation program improves students' level of knowledge. Case scenario training with a computer-based simulation is as effective as the classical method.

Keywords: Simulation, Computer-based, Undergraduate, Medical education, Advanced cardiac life support

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Introduction

Simulation is used for replacing real experiences and training in many fields, including medical education. With the development of technology, simulation methods also improved and became a growing trend. Distance learning, screen-based educational programs, and interactive learning environments gained increased importance. The use of simulation methods for medical education was investigated and integrated into the curriculum during the last few years, prominently for critical skills such as cardiopulmonary resuscitation. Simulator-mediated training is also recommended in the most recent cardiopulmonary resuscitation guidelines [1, 2].

The foremost concern of the interns in our country regards approaching an emergency patient and they feel insufficient both in theoretical and practical aspects [3]. Cardiopulmonary resuscitation is one of those subjects. Simulation-supported education is effective in teaching various algorithms and skills, and recent AHA and ERC guidelines emphasize the importance of using simulation techniques in cardiopulmonary resuscitation education. Many studies evaluate the effectiveness of simulation education alone; however, a few studies compare the different education methods with each other. With this study, we aim to assess the contribution of the simulation-supported education model on intern doctors' knowledge of ACLS rhythms and correct resuscitative approaches comparatively with today's classical education model.

Materials and methods

Eighty last-grade students who were working as interns in Gazi University Faculty of Medicine, Department of Emergency Medicine between February 15, 2017-April 30, 2017, were included in the study. Written consent was obtained from all participants. The students were divided into two equal groups, the control group, and the study group. Within the scope of ACLS training were arrest rhythms, tachycardia, and bradycardia. Two and a half hours of theoretical training was given to both groups before proceeding to case studies. Then, the same sample cases were shown, discussed, and solved with both groups; with a computer-based simulation program in the study group and with the classical didactic method in the control group. The participants were asked 25 multiple choice questions with a single correct answer to measure the level of knowledge, both before and 4 weeks after the training.

The questions were classified into 3 categories for thorough analysis:

Category 1 questions (simulation-direct): Questions consisting of the information in the scenarios shown with the simulation program

Category 2 questions (lesson): Topics included in the standard ACLS rhythms training, explained in the didactic phase of the lesson, but not included in the scenarios of the simulation program.

Category 3 questions (simulation- indirect): Rhythms are expected to be learned indirectly within the simulation program (arrest rhythms, bradycardic and tachycardic rhythms).

"ACLS Simulator 2016" licensed program, prepared by Anesoft Company, containing 12 scenarios per the ACLS guide of AHA (2015), was used on a single computer. Students solved the cases together interactively. The first 6 cases within the simulation program were about arrest rhythms and the last 6 cases regarded tachycardic rhythms.

Each case started with explaining the patient's clinical condition. The next screen simulated the patient's vital signs and heart rhythm. The students could see the patient's physical examination findings, administer a drug with chosen dose, make the decision on airway management (supportive oxygen supply, mask oxygenation, mask-valve mask ventilation, and endotracheal intubation), initiate and end cardiopulmonary resuscitation (CPR), and use the biphasic defibrillator to perform defibrillation and cardioversion with the desired joules.

Throughout the simulation, the students were expected to decide on the management and treatments in real-time, so there was a stopwatch in the upper left corner of the screen. Detailed information about the content and features of the program were explained to the students before starting the case studies. After a case was initiated, every step was decided by the students. By the end of the scenario, a special tab on the program screen revised the correct maneuvers and mistakes and revealed how the patient was managed. Later, the correct management of the simulated patient was discussed according to the ACLS guide.

Ethics committee approval for this study was obtained from the Ethics Committee of Gazi University (Date and number of documents: 09/02/2017 - E.20669).

Statistical analysis

Statistical analysis of the data was performed with SPSS (Statistical Package for Social Science, Chicago, II, USA) 19.0 program. Wilcoxon Signed Ranks Test was used to compare groups among themselves, and Mann-Whitney U test was used for inter-group analyses. Descriptive statistics included frequency, percentage mean, standard deviation, minimum and maximum values. The significance level was $P<0.05$ for all tests.

Results

Eighty medical students, 35 (43.75%) males and 45 (56.25%) females, with a mean age of 23.7 (1.1) years, were included in this study. There were 25 questions in the pre-training test, and the overall mean number of correct answers was 12.6 (3.2). While the study group answered a mean of 12.0 (3.3) out of 25 questions correctly, those in the control group answered 13.2 (3.2), which were similar ($P=0.131$).

The mean number of correct answers of the study and control groups in category 1, 2, and 3 questions in the pre-training test were 4.2 (1.6) and 4.7 (1.6) ($P=0.141$), 2.2 (1.0), and 2.8 (1.0) ($P=0.009$), 5.6 (1.6), and 5.6 (2.0) ($P=0.930$), respectively (Table 1).

Table 1: Comparison of the study and control groups before the training

	Study group	Control group	*P*-value
All questions	12.0 (3.3) (3-17)	13.2 (3.2) (4-20)	0.131
Category 1	4.2 (1.6) (0-7)	4.7 (1.6) (1-7)	0.141
Category 2	2.2 (1.0) (0-4)	2.8 (1.0) (0-5)	0.009
Category 3	5.6 (1.6) (3-9)	5.6 (2.0) (2-12)	0.930

The mean number of correct answers to the questions in the post-training test in both the study and control groups was

significantly higher compared to the pre-training test in all categories (P<0.001 for all).

In the post-training test, the study group answered 16.0 (3.6) questions correctly, while the control group answered 15.5 (3.1) (P=0.477). The mean number of correct answers of the study and control groups in category 1, 2, and 3 questions in the pre-training test were 4.9 (1.6) and 5.2 (1.5) (P=0.484), 3.5 (1.2), and 3.7 (0.8) (P=0.534), 7.6 (2.3), and 6.6 (1.7) (P=0.103), respectively (Table 2).

Table 2: Comparison of the study and control groups after the training

	Study group	Control group	*P*-value
All questions	16.0 (3.6) (7-23)	15.5 (3.1) (8-22)	0.477
Category 1	4.9 (1.6) (1-7)	5.2 (1.5) (2-7)	0.484
Category 2	3,5 (1.2) (0-5)	3.7 (0.8) (2-5)	0.534
Category 3	7.6 (2.3) (4-13)	6.6 (1.7) (2-10)	0.103

Discussion

According to our findings, adapting a computer-based simulation program improves students' level of knowledge. Our sample size of 80 participants is larger than many other studies in the literature [4-8]. Integrating simulation programs into the curriculum contributes to the student's level of knowledge and is as effective as training with the classical method. This result is similar to those of the previous studies. Among 64 students, Tan et al. [6] aimed to teach the management of anaphylaxis under the curriculum of "crisis management", and a significant difference was found under the category of "learning specific treatments" in the simulation group, trained with a computer-based simulation program. It was equally effective in classical resuscitation, diagnosis, and total score categories. In that study, students took the lectures in the second week of their internship, at the end of which post-training evaluation was performed. Similarly, a multicenter study conducted on 50 participants by Davis et al. [8] showed that training with a computer-based simulator is as effective as classical training. In this study, the post-training evaluation test was performed immediately after the training. However, the duration between pre- and post-tests was 4 weeks in our study, which reflects a longer-term effect of the education. Our study differs from other studies in the literature in this aspect.

In Biese et al.'s [9] study with 26 participants, there was no performance increase after simulation training. In contrast to this finding, our study showed that simulation education increases students' knowledge.

In the study group, after the lecture on ACLS rhythms, simulated cases were studied with the program "ACLS Simulator 2016". In this program, the objective is to learn to manage ACLS rhythms through 12 simulated cases. Arrest and tachycardia rhythms were discussed, each with 6 different case scenarios. There are no case examples of the bradycardic rhythms described in the ACLS manual, although they were covered in the lecture. This is a limitation of the program and our study. This is valid for the standard version of the program, however, in the institute-licensed version, it is possible to write your case scenarios and extend the content.

For this study, the simulation program was installed on a single computer and reflected on a big screen, and the cases were solved interactively. Simulated cases were discussed by the student group, the decision to be made at each step was commonly taken by all students. This way, a knowledge-sharing platform was created. Students expressed their opinions about the correct management steps and put forward their arguments to support them against other opinions. In this knowledge-sharing environment, the students also discussed how to analyze the clinical status and approach the simulated case. They observed each other's perspectives and approaches. Knowing how to manage a real patient is one of the biggest challenges for the students and interactive small-group training with simulated patients contributes to this skill.

An open-access simulation program that also enables multi-users may enable students to practice whenever they want. This could allow a higher number of students to take advantage of this training at any time, without the need for a separate classroom, instructor, and training period. This will help them reinforce their knowledge and practice. The findings of our study, which we conducted on a single computer license, are positive and promising despite all our limitations. Our study showed that a lecture reinforced with computer-based simulation is beneficial. More comprehensive studies on this subject may lead to the inclusion of these simulations in the standard education program.

Many studies in the literature showed that training with high-fidelity simulators is effective and they are the closest created environment to a real clinical situation. However, building up a simulation laboratory is tough. High-fidelity mannequins, extensive spaces, trained educators and personnel, and technical team are essential; a multi-disciplinary approach is needed. The number of students who can be trained simultaneously is exceptionally low compared to other simulation methods, creating a significant limitation, especially at the pre-graduate level. Due to the other requirements mentioned, it may not be possible to open a simulation center within the faculty or the hospital.

Screen-based simulation programs are cost-effective when used for training for appropriate skills, allowing students to practice on their own and repeat at any time. The feedback included in the programs gives the chance to see their mistakes. Thus, they can be directed to study more on that subject. All these aspects make the simulation programs suitable for more effective training.

Limitations

The major limitations of our study include the small number of participants and providing training on a specific subject only. Thus, our findings cannot be generalized to the whole medical education process. Also, our simulation training was performed in groups. Future research with a higher number of participants in which the computer-based simulation is made available for individual access, enabling repetitive training, may provide more accurate data.

Conclusion

We found no significant differences between the study and control groups after the training, which reveals that case scenario training with a computer-based simulation program is as effective as the classical didactic method. ACLS training with computer-based simulation can be an effective alternative in distance learning programs and in circumstances where face-to-face education cannot be performed.

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Research article

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Sensitivity and specificity of the modified tandem walking test for vestibular hypofunction with chronic dizziness in young adults

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Ethics Committee Approval
The study protocol was approved by the Ethics Committee of Marmara University Faculty of Medicine with the protocol number 092020633. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Patient comfort is greatly affected during videonystagmography (VNG), and more comfortable tests are needed for diagnosis. This study aims to evaluate the modified tandem walking test (MTWT) as an alternative pre-assessment method to the VNG test.
Methods: A total of 3348 patients were recruited in this retrospective cohort study between 2015-2019 based on the inclusion criteria of having chronic dizziness (>3 months), being aged between 18-65 years, and having an interpretable VNG test result. All patients were examined by an otolaryngologist, and the examination phase consisted of three parts: Physical examination, VNG test, and performing MTWT. The sensitivity, specificity, and likelihood ratio of the MTWT were calculated with the relevant formulas.
Results: The female/male ratio was 2.19, and there was no significant difference between the groups in terms of age (P=0.334). The number of patients who were VNG positive (regardless of MTWT), both VNG and MTWT positive, both VNG and MTWT negative, and VNG negative (regardless of MTWT) were 2519, 2000, 699, and 2519, respectively. The sensitivity and specificity of MTWT were 79.37%, and 84.31%, respectively.
Conclusion: MTWT has good sensitivity and specificity, and we think that it can be a safe, simple, and accessible pre-diagnostic tool when VNG is not available or cannot be tolerated by the patients.

Keywords: Vestibular hypofunction, Videonystagmography, Modified tandem walking test

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Introduction

Vestibular hypofunction patients have impaired dizziness, postural control, and instability [1]. Balance assessment is a major component of pre-diagnosis, because balance loss stems from vestibular system pathologies. Different tests can be used for balance assessment [2], and tandem walking (TW) is one of the most common. It is frequently used to evaluate balance disorders due to vestibular diseases; however, its sensitivity for vestibular diseases is poor [3, 4]. Therefore, the sensitivity and specificity of the modified version of the TW should be evaluated.

The ability of finding balance depends on inputs from the somatosensorial, visual, and vestibular systems [5], and functional vestibulospinal reflexes are required to maintain an upright position [6]. The MTWT allows the evaluation of balance problems in chronic dizziness using these reflexes.

Chronic dizziness is the most common symptom in vestibular problems such as vestibular hypofunction [7]. Many differential assessment methods are used to find the source of dizziness. VNG testing is the most important of these differential diagnostic tools and the gold standard for diagnosing and screening vestibular diseases [8, 9].

VNG is based on the functional examination of vestibulo-ocular reflex pathways by recording eye movements created by visual or caloric stimuli [10]. The caloric test is the fundamental part of VNG as a 'reference standard' in deciding vestibular hypofunction [11]. During this test, warm and cold water or air is delivered into the ear by the examiner. Although the bithermal caloric test provides detailed and quantitative data from patients with dizziness and balance problems by examining the function of the vestibular system, the test involves some physiological difficulty [12]. About 44% of people suffer from fatigue, 31% have nausea, and 33% have headaches during the test [13], which may exceed the tolerance limits of patients, rendering them unable to complete the test [14]. Also, bithermal caloric test is costly, time-consuming, and needs qualified staff. Therefore, we need simpler, accessible, and comfortable diagnostic tests.

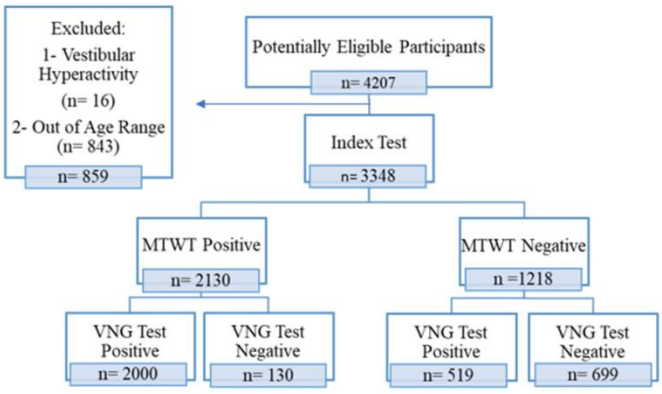
It is not known whether this test can be used instead of the VNG. Our hypothesis is that the MTWT can be used as an alternative pre-diagnostic assessment method in patients with vestibular hypofunction who have chronic dizziness.

Materials and methods

The study protocol was approved by the Ethics Committee of Marmara University Faculty of Medicine with the protocol number 092020633. The data in the patient files were evaluated retrospectively. Potentially eligible participants were taken to tests following self-reported complaints. The entire evaluation process was conducted by the same clinic and healthcare team between 2015-2019. Following the clinical history, all patients were taken to the VNG Caloric test and MTWT by the specialist. All patients were alert, cooperative, and able to follow commands during the assessment.

Inclusion criteria were (1) having chronic dizziness (>3 months), (2) being aged 18-65 years, (3) having an interpretable VNG test result. The individuals who (1) were diagnosed with benign paroxysmal positional vertigo or Meniere disease, (2) had an unclear psychological pathology or illness in the central nervous system, (3) were unable to stand independently, (4) had a visual impairment that can't be corrected with lens or glass, (5) had used medication for dizziness, (6) had a vestibular hyperactivity disorder, (7) had a history of orthopedic injury/surgery, (8) had missing data were excluded. This article adheres to STROBE criteria and the flow diagram is presented in Figure 1.

Figure 1: The flow diagram of the study



Videonystagmography Test: VNG - is the gold standard evaluation method for vestibular disorders. Bithermal caloric test is the most used form of the VNG test. It is the hardest as a technique, but most informative for diagnosis. The bithermal caloric test was conducted using the ICS Chart 200 VNG/ENG (otometrics) device. During the caloric test, patients laid in the supine position, and at 30° flexion to bring the horizontal semicircular canal to the vertical plane. The test was applied to both ears 5 minutes apart. The outer ear canal tympanic membrane was irrigated with 24°C air and 50°C air for 60 seconds, and 8 liters of air were consumed during the irrigation process. The highest value of the slow phase nystagmus velocity was calculated automatically with the Jongkees formula [15]. Channel paresis was accepted if the result was above 25%. The sum of the slow phase velocities formed with the cold and warm stimuli was less than 12 degrees/sec for complete paresis.

Modified Tandem Walking Test: Modification of tandem walking is challenging enough for the vestibular system simulation and testing. Every patient was shown the correct performance of the MTWT before they attempted it. Failures of MTWT included taking a sidestep or being unable to walk heel-to-toe with eyes closed. These failures were noted as a gross abnormality during MTWT. When the patient took a side-step, he/she started the next trial from scratch.

At the beginning of each trial, the patient stood in the Romberg test position with the feet together. The tandem walking test was modified by placing each palm on the opposite shoulder, and the elbows were kept parallel to the ground. Every patient was asked to walk on a straight line for ten steps forward, touching his/her heel of the front foot to his/her toe of the back foot with each step (heel-to-toe), wearing shoes, with arms folded across the chest and kept parallel to the ground, palms placed on the opposite shoulders. The trial involved performing the test once with eyes open, and thrice afterwards with the eyes closed. The test was considered negative when the patient opened his eyes or took a sidestep during the test. At least two

people were available near the patient during the test to provide manual assistance for safety when necessary [16].

Statistical analysis

Descriptive statistics were used for demographic variables with Statistical Package for the Social Sciences (SPSS v11.5). A 2x2 table was created to reflect the number of "MTWT positive", "MTWT negative", "VNG Test positive" and "VNG Test negative" patients. Methods for estimating measures of diagnostic accuracy were sensitivity, specificity, and likelihood ratio of MTWT.

Results

Among 4207 patients, the data of 3348 patients met the study criteria. Only young adults' data (18-65 years) were included to eliminate age-related loss of balance. Therefore, there is no drop-out data. However, patients with missing data were excluded from the study. Among females and males, 68.36% and 31.64% had positive VNG test results. The females were similar in terms of age (P=0.564) but the males significantly differed (P=0.009).

While 2098 patients had a unilateral weakness, 421 patients had a bilateral weakness according to VNG test results. The distribution of the gender-based age and classifications of vestibular hypofunction is shown in Table 1.

The sensitivity and specificity of the MTWT were 79.39%, and 84.31%, respectively. The positive likelihood ratio was 5.05, which indicates that despite every 5.05 persons are correctly diagnosed, one person is misdiagnosed. All results are presented in Table 2.

Table 1: Characteristics of Patients

Parameter		VNG Test (+) n	%	Mean (SD)	VNG Test (-) n	%	Mean (SD)	*P*-value*
Age	Female	1722	68.36	44.66 (12.41)	577	69.60	45.00 (11.81)	0.564
	Male	797	31.64	43.79 (11.85)	252	30.40	41.42 (12.63)	0.009
	P-value**	-		0.100	-		0.001	-
	Total	2519	100	44.38 (12.24)	829	100	43.91 (12.17)	0.334
Type of vestibular hypofunction	Left	1167	46.33	-	-	-	-	
	Right	931	36.96	-	-	-	-	
	Bilateral	421	16.71	-	-	-	-	
	Total	2519	100	-	-	-	-	

* Age differences of gender-based comparison between groups, ** Age differences of gender-based comparison in intra group analysis

Table 2: Coherence of sensitivity, specificity, and likelihood ratio of Modified Tandem Walk Test compared to VNG Test

	VNG Test (+)	VNG Test (-)	Total	Sensitivity (%)	Specificity (%)	Likelihood Ratio
MTWT (+)	2000 (a)	130 (b)	2130 (a+b)	79.39	84.31	5.05
MTWT (-)	519 (c)	699 (d)	1218 (c+d)			
Total	2519 (a+c)	829 (b+d)	2234 (a+b+c+d)			

MTWT: Modified tandem walking test, VNG Test: Videonystagmography Test, Sensitivity= (a/(a+c)), Specificity= (d/(b+d)), Likelihood Ratio= (sensitivity/(1-specificity))

Discussion

Dizziness is one of the most common symptoms that occur due to middle ear pathologies. The early detection of pathology in the vestibular system facilitates the rehabilitation process. For this reason, there is a need to develop usable, and accessible evaluation methods which help to keep patient comfortable. According to our results, the MTWT had good sensitivity and specificity, similar to those of the VNG test in patients with vestibular hypofunction.

A tandem walking test is frequently used by clinicians and usually performed with the eyes open. However, studies have reported that the test assesses balance better without visual feedback. The fact that the test can be performed in a short time and is suitable for pre-evaluation increases its clinical importance and allows the review of advanced examination options based on its results. Because the optimal cut-point is 2 steps, requirements are minimum for performing the test. On the other hand, evaluators must be careful because the strategies that individuals develop to maintain balance are different from each other. Therefore, its use as an alternative evaluation method will alleviate the burden of the clinicians.

The VNG test, which provides detailed and quantitative data by examining vestibular system function, has its own temporal and physiological difficulties [12, 17]. Most patients cannot complete the test due to symptoms such as dizziness, nausea, vomiting, and sweating [14]. Therefore, the development of more comfortable alternative diagnostic tests instead of the VNG test will facilitate patients' comfort and clinic conditions. The MTWT is a simple assessment test that can help identify an early diagnosis of vestibular disorder. In this study, we evaluated the sensitivity and specificity of the modified tandem walking test to support the VNG test results and help assist in making a preliminary diagnosis.

Based on our results, the MTWT is shorter, cheaper, comfortable, and easier to apply than the VNG test, with 79.39% sensitivity, 84.31% specificity, and 5.05% positive likelihood ratio. There are different rapid screening tests used in the clinic. A retrospective study reported a correlation between the head thrust test, and the dizziness disability inventory. In the same study, the VNG test was considered the reference for unilateral vestibular hypofunction patients, and the sensitivity, and specificity of the head thrust tests were 31%, and 96%, respectively. The head thrust test has enough sensitivity to be used as an uncompensated vestibulopathy screening [18]. A different study reported that tandem walking test, walking with head turns and functional mobility tests were unable to detect vestibular problems [19].

Another easy-to-apply screening test is the head-shaking test. In one study, patients with unilateral hypofunction and benign paroxysmal positional vertigo (BPPV) had lower head-shaking test results than healthy individuals. When the completion duration of the functional mobility test in subjects diagnosed with unilateral vestibular hypofunction was evaluated, it was observed that they took longer steps than healthy individuals. Besides, the number of eyes-closed steps of individuals in the same disease group was evaluated by the tandem walking test, and it was found that these patients took fewer steps than healthy people. However, the sensitivity of the tandem test with eyes open was very low, at 14%. When the same test was repeated with the eyes closed, its sensitivity was relatively higher at 23%. According to the ROC analysis results of the tandem test, if the person can take five or more steps in the open eye test, the sensitivity of the test is 14%, and the specificity is 99%. Likewise, when the test was performed with the eyes closed if the person can only take two or fewer steps, the

sensitivity was 23%, and the specificity was 92%. It is suggested that clinicians can use the tandem walking test only to assist other tests, not for a diagnosis. Also, some state that this test would be more suitable for use in the performance evaluation of previously diagnosed patients [19]. Another study investigated the usability of tandem walking as a rapid screening test for vestibular diseases. Ninety patients diagnosed with vestibular dysfunction and 292 healthy individuals were included in the study. The tandem walking test had 77% sensitivity and 72% specificity in patients diagnosed with a vestibular dysfunction under 50 years of age [3].

The BPPV patients had impaired performance on tests of standing balance and subjective visual vertical [20–22]. This impairment is caused by the effects of vestibular nucleus signal changes on loading of the posterior semicircular canal and unloading of the utricles. Step counts in tandem test are useful in detecting changes in dynamic postural stability [23]. The test is useful for examining motor performance, treatment effectiveness, time-dependent changes, and primary care physicians for assessing the influence of rehabilitation interventions.

Clinical challenges in VNG testing practice encourage the research and development of alternative assessment methods. We used the test for this purpose and found that it had a higher level of sensitivity and specificity than other field tests used to evaluate individuals with vestibular hypofunction. Because this test is useful, easy to apply, less time-consuming than the VNG test, and has sufficient specificity and sensitivity, we think that it can be appropriate for preliminary diagnosis.

Limitations

We presented real-time clinical data. While collecting these data, the primary aim was to determine whether the treatment outcome of our patients was positive. Therefore, MTWT results were reported as positive/negative, and the number of steps was ignored. Since our sample size was large and the results had significant sensitivity and specificity, it was deemed appropriate to share the data. Determining the cut-off value by recording the number of steps will contribute to the widespread clinical use of the test in future studies.

Conclusion

Our results suggest that MTWT can be used for preliminary diagnosis in clinical conditions where there is no VNG test. It can be widely used in clinics due to its ease of practice, accessibility, and simple nature; therefore, the evaluator can perform the test without the need for more instruction. It can provide fast, low-cost, and reliable results. However, the cut-off values need to be determined for patients with vestibular hypofunction and should be used as reference values in order to share the results of treatment efficacy in future studies.

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The relationship between blood pressure regulation and alexithymia variability in newly diagnosed essential hypertension patients

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Ethics Committee of Bilecik Provincial Health Directorate, 15.04.2020 (Number: 2020/016). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Blood pressure disorder can accompany mood and various psychosomatic disorders. One of the signs of emotional disorganization is alexithymia, which is defined as the impaired ability to experience and express emotions. The relationship of hypertension (HT) with alexithymia is well known, but few studies show the change in alexithymia status after blood pressure regulation. Our study aimed to evaluate the level of alexithymia caused by optimal medical treatment in newly diagnosed essential HT patients.

Methods: Fifty-six essential HT patients (33 males, 23 females) diagnosed with 24-hour ambulatory blood pressure monitoring were included in this cross-sectional study. All participants filled the Toronto Alexithymia Scale (TAS-20) during diagnosis and when blood pressure was regulated with treatment.

Results: The mean age of the study group was 50.7 (9.9) years. There were twenty-three (41.1%) females. As expected, the systolic and diastolic blood pressure values were significantly lower after treatment (144.41 (9.11) / 89.42 (9.31) mmHg vs. 122.75 (7.27) /74.96 (3.18) mmHg, $P<0.001$ for both). While TAS-DIF (difficulty identifying feelings) and TAS-EOT (externally oriented thinking) did not significantly change after treatment, a significant decrease was observed in TAS-DDF (difficulty describing feelings) (14.29 (3.51) vs 12.57 (3.06), $P<0.01$). Total TAS score, TAS-20, was also significantly decreased after treatment (55.67 (8.82) vs 52.35 (7.71), $P=0.036$).

Conclusion: Our findings show that TAS-DDF, one of the subscales of alexithymia, can be improved by regulating blood pressure. We think that psychiatric and emotional states should be evaluated in the follow-up of HT. It is also essential to increase the awareness of patients about coping with stress and stress management.

Keywords: Alexithymia, Essential hypertension, Blood pressure regulation, Toronto Alexithymia Scale

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Introduction

Hypertension (HT) is a global, common health problem that affects approximately 1.13 billion people [1]. It is a significant cause of mortality and morbidity due to its direct and indirect cardiovascular and neurovascular complications [2]. Etiologically, it is examined in two main groups. Essential (primary) HT is the most common cause and constitutes 95% of the cases [3]. The others are secondary causes. The etiology of essential hypertension is multifactorial. Many studies showed that negative psychological conditions both increase blood pressure and cause newly diagnosed hypertension [4-6]. These include anger, anxiety, depression, acute stress, the effect of negative emotions, and Type D personality, such as many psychiatric conditions [7, 8]. In such psychiatric problems, disorders in the autonomic nervous system assume a part in the pathogenesis of HT. There is also alexithymia among the psychological dimensions investigated in connection with HT [9-11].

Alexithymia is a versatile and transdiagnostic condition characterized by a complex and externally oriented way of thinking and recognizing and distinguishing emotions. It has a prevalence of 7-10% in the general population [12, 13]. Numerous studies investigated the relationship between HT and alexithymia with different results. Some authors reported a significant relationship, others reported a mild one, while a small number of studies reported none [14-16]. The auscultatory technique traditionally used in blood pressure assessment can yield incorrect results in psychosomatic cases and show an instant value. Ambulatory blood pressure monitoring (ABPM) enabled 24-hour blood pressure measurement and recognition of white coat HT and masked HT [17].

Our study aimed to compare the pre-treatment and post-treatment alexithymia levels in patients with a newly diagnosed HT with ABPM.

Materials and methods

Study population

The data of sixty-five patients with newly diagnosed HT between the ages of 18-65 years who visited the cardiology and nephrology outpatient clinics between March 2020 and June 2020 were reviewed. Patients diagnosed with HT for the first time with ABPM who received two months of medical therapy and had regulated blood pressure in control visits met the inclusion criteria. Control blood pressure analysis was performed with 24-hour ABPM. Nine patients were excluded from the study because optimal blood pressure values could not be achieved. In total, 56 patients were included in this cross-sectional study. TAS scale was filled by all participants at the time of HT diagnosis and after antihypertensive treatment for at least two months.

We excluded those with the following criteria:

- Antihypertensive drug use in the last six months
- Known coronary artery disease and myocardial infarction
- Heart failure (LVEF <50%)
- Valvular heart disease (moderate or severe)
- Systemic and secondary HT
- Diabetes mellitus (Types 1 and 2)
- Chronic renal failure (GFR <60 ml / min)
- Chronic pulmonary disease (COPD, asthma, etc.)
- Pulmonary HT (sPAB > 25 mmHg)
- Hemoglobin <11 gr / dL
- Active infection
- Atrial fibrillation
- Neurological and psychiatric disorders
- Patients in which blood pressure could not be regulated with medical therapy.

General assessment and laboratory measurements

A complete physical examination was performed on all participants included in the study, a detailed medical history was obtained, and the findings were recorded. Patients' demographic information, sociocultural levels, lifestyles, medical and psychiatric information were collected through face-to-face interviews. Participants' blood pressure was measured using the traditional auscultatory technique in the initial assessment. Measurements were obtained from both arms with the feet touching the ground, after at least 15 minutes of rest. Height, weight, and waist circumference were measured. Body mass index (BMI) was calculated using the formula [weight (kg) / height (m^2)].

After 12 hours of fasting, venous blood samples were obtained from all participants for a complete blood count and biochemical analysis. A urine sample was obtained for complete urinalysis. The biochemical analysis included fasting blood glucose, kidney function tests, liver function tests, lipid profiles, thyroid hormones, albumin, protein, and serum electrolytes. Protein, glucose, leukocyte, and urine crystals were analyzed in the urine. Renal and color Doppler ultrasound were performed on all participants to investigate secondary HT. Conventional echocardiographic evaluation was conducted in the entire study group in the left lateral decubitus position. Suprasternal imaging was performed to investigate the presence of aortic coarctation. EPIQ 7 echocardiography device (Philips, Amsterdam, the Netherlands) was used for echocardiographic evaluations.

Ambulatory blood pressure monitoring

Ambulatory blood pressure measurements were performed with a measuring device (GE CardioSoft Tonoport V) that conformed to the ESC / ESH guideline criteria. It was measured every half hour during the day and every hour at night. Standard device settings were used between 08:00-22:00 for daytime measurements and between 22:00-08:00 for night measurements. Blood pressure values were evaluated according to the ESC / ESR guidelines. The diagnostic threshold for hypertension was a mean value of ≥130 / 80 mmHg for 24 hours, 135/85 mmHg during the day, and 120/70 at night [17]. In the comparison of nighttime systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) measurements with daytime averages, those with> 10% nocturnal drops were defined as dipper, and 10% or fewer declines were defined as non-dippers.

Toronto Alexithymia Scale

Toronto Alexithymia Scale (TAS) is a Likert-type self-assessment scale consisting of twenty items, scored between 1 and 5 (1=never, 5=always), used to evaluate the level of alexithymia of the individual [18]. Items 4, 5, 10, 18, and 19 are scored in reverse. The scale consists of three subscales:

Difficulty identifying feelings (DIF), difficulty describing feelings (DDF), and externally oriented thinking (EOT).

- TAS DIF: The difficulty identifying feelings sub-scale consists of seven items (1, 3, 6, 7, 9, 13, and 14) is defined as difficulty in identifying emotions and distinguishing them from bodily sensations that accompany emotional arousal.
- TAS DDF: The difficulty describing feelings subscale consists of five items (items 2, 4, 11, 12, and 17) and is defined as difficulty conveying emotions to others.
- TAS EOT: The externally oriented thinking subscale consists of eight items (items 5, 8, 10, 15, 16, 18, 19, and 20). The presence of an extrovert cognitive structure is defined as the weakness of introverted thinking and imagination power.

Participants are asked to mark one of the options, such as never, rarely, sometimes, often, and always. A high score indicates increased alexithymia. In the Turkish version used in this study, the cut-off score was 59 to identify individuals with alexithymia [19]. Scores are interpreted as follows: <50 points: No alexithymia, 51-60 points: Possible alexithymia, > 61 points: Definite alexithymia.

Statistical analysis

In the statistical analysis of the data, numerical variables were expressed as arithmetic mean (standard deviation) and categorical variables as percentages. The one-sample Kolmogorov–Smirnov test was used to determine whether the numerical variables showed a normal distribution. For assessing differences between groups, the Student t-test was used for normally distributed parameters, while the Mann-Whitney U test was used for non-normally distributed parameters. Spearman's correlation test was used to evaluate the existence of a linear relationship between non-normally distributed parameters. The presence of a linear relationship between normally distributed parameters was assessed with Pearson's correlation test. $P<0.05$ showed statistical significance. IBM SPSS for Windows (Version 22.0. Armonk, NY: IBM Corp.) was used for data analysis.

Ethics

After informing all participants about the study, a written informed consent form was obtained from those who volunteered to participate. The study was conducted according to the principles of the Helsinki Declaration. Local ethics committee approval was received for this study from Bilecik Provincial Health Directorate (No: 2020/016).

Results

The study included a total of 56 individuals, 23 females (41.1%) and 33 (58.9%) males. The mean age of the study group was 50.7 (9.9) years. Among all, 76.8% were married. The intermediate education level was 7.3 (4.2) years. Most patients resided in the city center (62.5%). The number of people working in a specific profession for at least the last six months was 44 (78.6%), while 12 (21.4) individuals were unemployed. The mean BMI of the participants was 28.3 (4.6) kg/m^2. The TAS-20 scale scores of 16 (28.6%) subjects were ≥61, those of 18 subjects (32.1%) were between 50-61, and those of 22 subjects (39.3%) were below 50 before the treatment. The demographic, anthropometric, and sociocultural information of the patients is presented in Table 1.

Table 1: Demographic, anthropological, lifestyle and psychological variables

Variables	Study group (56) Mean (SD)	n	%
Age (years)	50.7 (9.9)		
Gender	Female	23	41.1
	Male	33	58.9
Height (cm)	169 (12.6)		
Weight (kg)	76 (11. 6)		
BMI (kg / m^2)	28.3 (4.6)		
Smoking	User	21	37.5
	Not user	35	62.5
Marital status	Married	43	76.8
	Single	13	23.2
Education level	Literate	6	10.7
(Mean: 7.3 (4.2) years)	Primary education	25	44.6
	High school	18	32.2
	University	7	12.5
Living place	Rural	8	14.2
	County	13	23.3
	Province	35	62.5
Working Status	Working	44	78.6
	Not working	12	21.4
TAS-20 point	≥ 61	16	28.6
	50 – 60	18	32.1
	≤ 50	22	39.3

SD: Standard deviation, BMI: Body mass index, TAS-20: Toronto Alexithymia Scale- 20

The SBP and DBP values significantly decreased in the post-treatment group (144.41 (9.11) / 89.42 (9.31) vs 122.75 (7.27) / 74.96 (3.18), $P<0.001$ for both) compared to pre-treatment. While there was no significant difference for TAS-DIF (19.30 (5.49) vs. 18.14 (4.49), $P=0.215$) and TAS-EOT (22.09 (3.44) vs. 21.64 (3.75), $P=0.514$) in TAS scale evaluation, significant decreases were observed in TAS-DDF (14.29 (3.51) vs 12.57 (3.06), $P<0.01$) and TAS 20 with treatment (55.67 (8.82) vs. 52.35 (7.71), $P=0.05$). Pre-treatment and post-treatment mean blood pressure and TAS scale comparisons are shown in Table 2.

Table 2: Comparison of pre-treatment and post-treatment 24-hour ABPM blood pressure values and TAS scale

Variables	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	*P*-value
SBP (mmHg)	144.41 (9.11)	122.75 (7.27)	<0.001
DBP (mmHg)	89.42 (9.31)	74.96 (3.18)	<0.001
TAS-DIF	19.30 (5.49)	18.14 (4.49)	0.215
TAS-DDF	14.29 (3.51)	12.57 (3.06)	0.01
TAS-EOT	22.09 (3.44)	21.64 (3.75)	0.514
TAS-20	55.67 (8.82)	52.35 (7.71)	0.05

SBP: systolic blood pressure, DBP: diastolic blood pressure, TAS: Toronto Alexithymia Scale, DIF: difficulty identifying feelings, DDF: difficulty describing feeling, EOT: externally oriented thinking

Discussion

We showed that the level of TAS-DDF and the total TAS-20 score significantly decreased by providing blood pressure regulation with medical treatment in newly diagnosed essential HT patients. The primary goal of this study was to investigate the association between hypertension and alexithymia, considering drug therapy and focusing on other aspects of hypertension.

While psychosomatic studies on hypertension focus particularly on anxiety, anger, and negative emotional reactions, the number of studies conducted to evaluate the relationship between emotions that are not consciously recognized is limited [6, 20, 21]. In our study, the relationship between blood pressure regulation and the level of alexithymia, which is a personality concept, was evaluated. Several previous studies report a strong relationship between HT and alexithymia. In the studies of Todarello et al. [15] and Grabe et al. [9], alexithymia was an independent risk factor for HT. We got similar results on the

total TAS-20 scale. These studies differed from ours in that only the total alexithymia level was evaluated.

On the other hand, we included three different subscales of alexithymia in our study and found that TAS-DDF was also associated with high blood pressure. We consider this an important finding. Significant differences among TAS-20 subscales emphasize the importance of the dimensional character of alexithymia and further strengthen the need for factor-based approaches in alexithymia research. Another different and superior aspect of our study was that 24-hour ABMP was used instead of the general auscultatory technique in HT. In this way, masked HT and white coat HT were largely excluded. Again, in an old study conducted in 1999, emotional improvements were observed in treated HT patients [14]. In this study, the TAS-20 scale, which is the previous version of the current TAS-26 scale, was used. We used the current version and the Turkish version [19].

In the literature, the incidence of alexithymia, which is around 10%, is reported to increase up to 55-65% among HT patients [22-24]. In our study, the probable and exact rate of alexithymia was around 60% in newly diagnosed patients who had not yet started antihypertensive drugs. The actual and possible percentage of alexithymia was close to that in the literature.

Alexithymia was associated with physiological conditions that can lead to medical diseases [25, 26). It was reported that the level of alexithymia is higher in some chronic, autoimmune and systemic diseases compared to the average population [27-29]. A larger study investigating the relationship between alexithymia and metabolic syndrome (MetS) reported that the rate of alexithymia was significantly higher in patients with MetS. In this study, it was significantly associated with waist circumference, triglycerides, and HT [30]. In a recent study, hypertensive patients were more alexithymic than normotensive participants, similar to other studies [10]. However, treated hypertensive patients were more alexithymic than normal and untreated patients. In our study, we found that blood pressure regulation reduces alexithymia. We think that the different results may be due to the socio-cultural differences of the patient populations. The anxiety of having a chronic illness and its psychological dimension may have various consequences for societies. The person feels safe by being treated or, on the contrary, having a chronic disease and the necessity to receive long-term medical treatment and the expected lifestyle change may affect the level of alexithymia differently.

The study has some limitations. The first and main limitation of the study was the few numbers of participants and the relatively short follow-up time. Another limitation was that the research was conducted in a single center.

Conclusions

Our findings further back the hypothesis that alexithymia is linked with hypertension. TAS-DDF, one of the different dimensions of alexithymia, seems to be the most important feature that explains this connection. In many chronic diseases such as HT, alexithymia is more common than in the normal population. Still, we showed that this rate can be reduced with blood pressure regulation after optimal treatment. In the follow-up and treatment of HT, we think that the psychiatric conditions of the patients should also be investigated, psychological support should be obtained when necessary and this should be a part of the treatment. There is a need for future studies on the subject with larger populations and longer follow-up periods.

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The effectiveness of the Ambu® AuraGain™ laryngeal mask on hemodynamic and respiratory parameters in patients undergoing septoplasty: A randomized prospective clinical study

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Ethics Committee Approval
Adıyaman University Biomedical Research Ethics Committee approval was obtained from the ethics committee dated 28.04.2015 and numbered 2015 / 03-14.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: The use of laryngeal masks is increasing with the introduction of 3rd generation airway vehicles. However, endotracheal intubation is preferred by most anesthesiologists in septoplasty operations due to airway safety concerns. In this study, we aimed to compare the 3rd generation airway device, Ambu® Auragain ™ LMA, with tracheal intubation in terms of hemodynamic and respiratory parameters.
Methods: This study included 69 patients aged 18–60 years with an ASA score of 1–2 who were scheduled for septoplasty in Adıyaman University Research and Educational Hospital between 2016.01.01 and 2017.06.31. Study groups were randomly defined as Group 1 - Ambu® AuraGain™ laryngeal mask (LMA, n = 37) and Group 2 - endotracheal intubation (ETT, n = 32), and the hemodynamic and respiratory parameters were measured and recorded.
Results: The demographic data and partial oxygen saturation of the patients were similar ($P>0.05$ for all values). The patients in the ETT group had a higher heart rate at induction, intubation and at the first minute compared to the LMA group ($P<0.05$ for all values). The mean arterial pressure was significantly lower at induction, intubation, at minutes 1, 2, 3, and 4 of intubation, and at extubation in the LMA group ($P<0.05$ for all values).
Conclusion: The Ambu® AuraGain™ laryngeal mask was similar to or better than tracheal intubation in terms of hemodynamic and respiratory parameters. The Ambu® AuraGain™ LMA can be used as an equivalent to tracheal intubation in terms of hemodynamic and respiratory parameters.

Keywords: Ambu® AuraGain™ laryngeal mask, Tracheal intubation, Septoplasty

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Introduction

Endotracheal intubation is conventionally preferred for septoplasty operations due to concerns about contamination of the tracheobronchial tree by surgical bleeding and risk of damage to the airway by displacement during surgical maneuvers. However, the introduction of the new generation of laryngeal mask airways (LMA) has led to increasing use in head and neck surgeries such as septoplasty due to their higher seal and full adaptation to the trachea's anatomy [1, 2].

The Ambu® AuraGain™ (Ambu A/S, Ballerup, Denmark), a third-generation airway device, is made of polyvinyl chloride and, thanks to its curved structure, is compatible with the anatomy of the respiratory tract [3]. This structure provides a higher seal. It has a gastric tube for gastric aspiration and allows the endotracheal tube to pass through it, thus allowing for blind intubation or fiberoptic use [2, 3].

The goal of our investigation was to compare the Ambu® AuraGain™ LMA and an endotracheal tube (ETT, Bıçakçılar, İstanbul, Turkey) on hemodynamic and respiratory parameters in patients undergoing septoplasty.

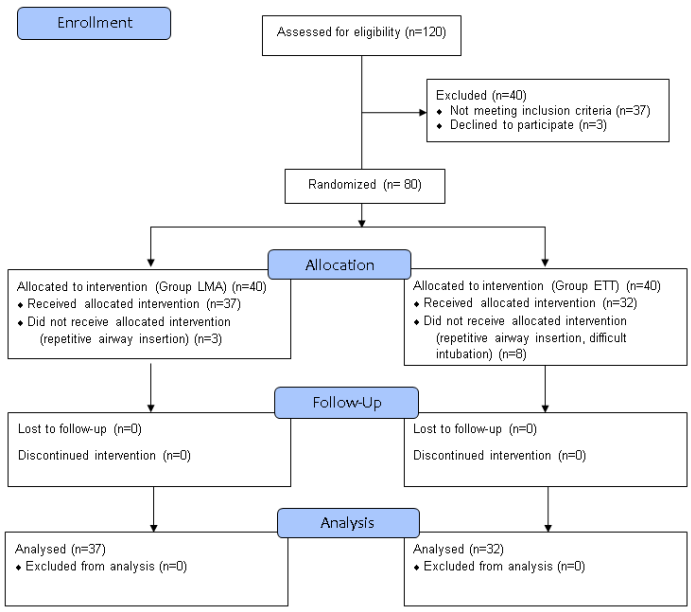
Materials and methods

This randomized, prospectively controlled, equivalence study was approved by Adıyaman University Chairmanship of Biomedical Research Ethics Committee (no. 2015/03-14, dated 2015.04.28). The minimum sample size of the study was calculated as 30 individuals in each group, with an alpha error level of 0.05 and a test strength (beta) of 0.8, taking previous studies on the subject as reference [4]. The study included 69 patients aged 18–60 years with an American Society of Anesthesiologists (ASA) score of 1–2 who underwent septoplasty at Adiyaman University Training and Research Hospital between 01 January 2016 and 31 June 2017 and was conducted in accordance with the Helsinki Declaration. The report follows the Consolidated Standards of Reporting Trials (CONSORT). Because possible risks such as bronchospasm, bleeding risk, dental damage, etc. would affect the study data, patients with difficult intubation risk, a Mallampati score of 3–4, a body mass index (BMI) >30 kg/m^2, a short neck, thyromental distance <60 mm, mouth opening <25 mm, a history of obstructive sleep apnea, and those with respiratory, cardiac, renal, and hepatic diseases were excluded from the study. Due to the nature of the study, repetitive trials were not allowed. Patients undergoing repeated trials were excluded from the study, as it may affect hemodynamic and respiratory parameters. The references used for the study were scanned using PubMed, Google Academic, Scopus, and index Copernicus.

The patients were randomly assigned into ETT (n:32) and LMA (n:37) groups by a nurse blinded to the study using the sealed envelope method. All participating patients gave informed consent prior to the operation and were preoperatively evaluated by an anesthesiologist. All the procedures were performed by experienced anesthesiologists. The patients were placed on the operating table without any sedation after a proper fasting time and monitored by pulse oximetry, non-invasive blood pressure, and electrocardiogram (ECG). The time from the handling of the airway device to the observation of the capnography waveform was considered the insertion time. All patients were preoxygenated for 5 minutes (100% 4–6L O_2). In the ETT group, anesthesia was induced with intravenous propofol (2 mg/kg^{-1}; Polifarma, Istanbul, Turkey), fentanyl (1 mcg/kg^{-1}; Vem, Istanbul, Turkey), and rocuronium (0.6 mg/kg^{-1}; Polifarma, Istanbul, Turkey), and an endotracheal tube of appropriate size was placed. In the LMA group, induction was performed using intravenous propofol (2 mg/kg^{-1}), fentanyl (1 mcg/kg^{-1}), and rocuronium 0.2 mg/kg^{-1}, and an Ambu ® AuraGain™ LMA (Ambu, Ballerup, Denmark) was placed. After making sure there was no air leak, both lungs were ventilated, and seeing the capnography waveform, the patient was connected to the anesthesia device (Primus^{TM} Drager, Drager Medical Gmnp, Lübeck, Germany). Mechanical ventilation was adjusted as follows: Tidal volume of 6–10 mL/kg, end-tidal carbon dioxide ($EtCO_2$) of 35–45 mmHg, and a respiratory rate of 10–14 min^{-1}. Oropharyngeal seal pressure was set to a flow rate of 3 L/min and Adjustable Pressure Limitation (APL) pressure was set to a maximum pressure of 40 cmH_2O. Anesthesia was preserved with an admixture of sevoflurane (Abbott, Istanbul, Turkey) and 50% air–oxygen at a minimal alveolar concentration (MAC) of 1. At the end of the operation, the anesthetic agent was discontinued, and ventilation was provided with 100% oxygen. Following spontaneous breathing, neostigmine (0.04 mg/kg^{-1}; Adeka, İstanbul, Turkey) and atropine (0.02 mg/kg^{-1}; Biofarma, İstanbul, Tukey) were intravenously (IV) administered. The patients with a modified Aldrete's score of 9 or above who achieved a sufficient tidal volume were extubated. Tramadol 100 mg was used for postoperative pain management.

The patients' demographic data and procedural complications were recorded. Their vital findings were measured preoperatively, at intubation, at 1, 2, 3, 4, 5, 10, 15, 20, and 30 minutes post-intubation, and at extubation. End-tidal carbon dioxide ($EtCO_2$) and airway pressures were perioperatively recorded. The consort flow diagram applied for patient selection is shown in figure 1.

Figure 1: CONSORT 2010 flow diagram



Statistical analysis

IBM SPSS Statistics version 21.0 (IBM Corp, Armonk, NY, USA) software was used for statistical analyses and calculations. The level of statistical significance was set at

P<0.05. Number (n) and percentages (%) were used to demonstrate the distribution of demographic information, such as gender, age, BMI, and time of insertion. Continuous variables were analyzed using Student's t-test, the Mann-Whitney U test, and the chi-square test. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used for normality of distributions and normal distribution. The ANOVA test was used for the analysis of repeated measurements.

Results

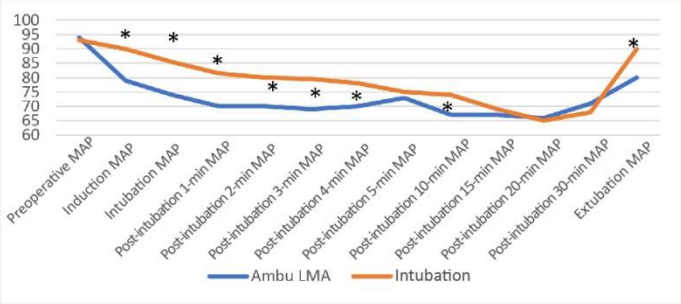
The mean age and BMI of 69 patients, 49 (71%) of which were male, were 27.1 (9) years, and 23.9 (2.7) kg/m^{2,} respectively. The groups had similar characteristics in terms of demographic data (Table 1). The insertion times were 13 (5) seconds in the LMA group and 50 (15) seconds in the ETT group. Three patients in the ETT group developed nausea, and 1 patient in the LMA group developed a cough.

The analysis of heart rates showed significant elevations in the ETT group at induction, intubation, and at 1 minute post-intubation (*P*=0.002, *P*=0.001 and *P*=0.022, respectively). The groups had similar heart rates at the other time measurements. Mean arterial pressure (MAP) showed a significant reduction in the LMA group at induction, at minutes 1, 2, 3, 4, and 10 post-intubation, and at extubation (*P*<0.001, *P*=0.003, *P*=0.004 *P*=0.002 *P*=0.002, *P*=0.008 *P*=0.024 and *P*=0.01, respectively). The other values measured at the other time points were similar between the groups. The MAP measurement data are presented in Figure 2.

Table 1: Demographic data

	Group LMA n :37	Group ETT n:32	Total n :69	*P*- value
Age	26.7 (9.4)	27.7 (8.7)	27.1 (9.0)	0.510
Gender (Male)	28 (75.6%)	21 (61.6%)	49 (71%)	0.515
BMI	23.8 (2.9)	24.0 (2.3)	23.9 (2.7)	0.745

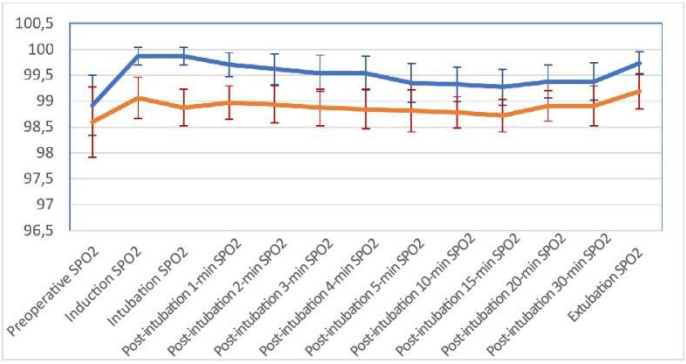
Figure 2: Change in median MAP values of patients by time



* There is a statistically significant difference between the groups. *P*<0.05

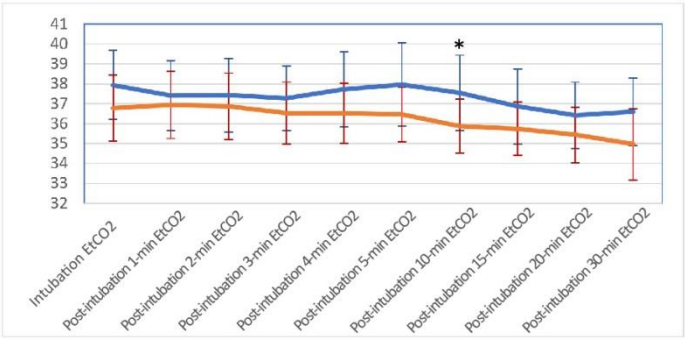
$SatO_2$ values differed significantly between the groups at all times except for the preoperative measurement. The LMA group had higher $SatO_2$ values (*P*<0.05 for all values) (Figure 3). The analysis of the end-tidal CO_2 data indicated a similarity between the groups at all time points (*P*>0.05 for all values), except for the 10th minute post-intubation (*P*=0.017) (Figure 4). The measurement of airway pressures showed higher airway pressure in the ETT group at all times (*P*<0.05 for all values) (Figure 5).

Figure 3: Change in mean and standard deviations of SPO2 values of patients by time



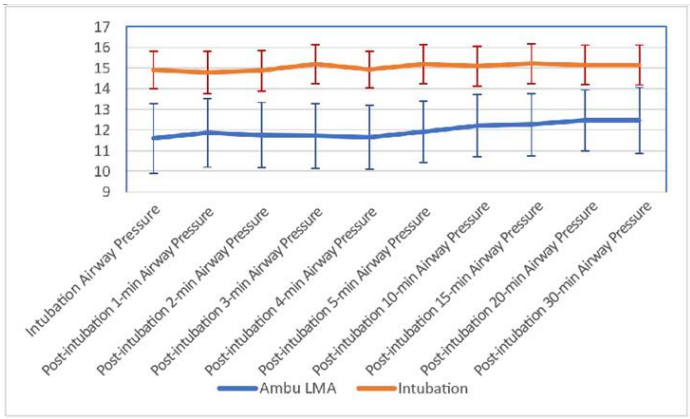
* There is a statistically significant difference between the groups at all times except for preoperative values. (*P*<0.05) Orange line: intubation; blue line: LMA.

Figure 4: Change in mean and standard deviations of EtCO2 of patients by time



* There is a statistically significant difference between the groups. (*P*<0.05) Orange line: intubation; blue line: LMA.

Figure 5: Change of mean and standard deviations of airway pressure values of patients by time



* There is a statistically significant difference between the groups at all times. *P*<0.05

Discussion

The data obtained in our study revealed that Ambu® AuraGain™ LMA was equivalent to endotracheal intubation in septoplasty operations in terms of hemodynamic and respiratory parameters.

Since the airway is in the surgical area during septoplasty operations, anesthesiologists generally prefer endotracheal intubation due to safety concerns. With the introduction of new-generation airway devices, better sealing pressure has been achieved during positive pressure ventilation. The Ambu® AuraGain™, a third-generation airway device, provides higher sealing pressure with its curved silicon structure. In our study, the Ambu® AuraGain™ group had lower airway pressures throughout the entire septoplasty operation. This result can be considered an indication that LMA provides sealing even at higher pressures. Karaaslan et al. [5] compared the LMA Supreme and ETT in patients undergoing septoplasty and found that LMA provided more protection in preventing blood leak. Al-

Mazrou et al. [6] concluded that LMA may be preferred as an alternative to ETT for pediatric patients undergoing sinusoidal surgery. Lee et al. [7] found that ventilation decreased with head and neck movements and that effective ventilation could be provided in a neutral head position with LMA. A study by Mihara et al. [8] on pediatric patients concluded that the i-Gel® (Intersurgical Ltd., UK, second generation) was easier to place than the Ambu® AuraGain™ and therefore caused less oropharyngeal damage, but lower airway pressures were obtained with the Ambu® AuraGain. Likewise, Uthaman et al. [9] found that use of the Ambu® AuraGain™ LMA in patients with an immobilized cervical spine had adequate oropharyngeal leak pressure with a stiff collar. Although studies on the third-generation airway device, the Ambu® AuraGain™ LMA, are more limited, most studies performed with other LMA variants showed that the Ambu® AuraGain™ LMA is equivalent or superior to LMA [7, 10, 11].

Another feature of the Ambu® AuraGain™ LMA is that it allows ETT to pass through. It is advantageous to switch to ETT due to difficult intubation or laryngeal pressure in prolonged operations. Many studies were conducted on this subject [12, 13]. However, when Schiewe et al. [14] compared the laryngeal mask Fastrach™ (Teleflex Medical, Dublin, Ireland. second generation) with the Ambu® AuraGain™ in terms of blind intubation, they concluded that the laryngeal mask Fastrach™ was more successful. Since our study aimed to compare the effectiveness of Ambu® AuraGain™ LMA with tracheal intubation in septoplasty cases, this feature of LMA was not evaluated.

Studies on Ambu® AuraGain™ LMA generally found that it was similar or superior to ETT in terms of hemodynamic data [5, 12, 15]. The analysis of heart rates in our study showed higher values in the ETT group at intubation. This can be explained by the sympathetic activation caused by the laryngoscope. There was no difference in the measurements at the other time points. The Ambu® AuraGain™ LMA group had significantly lower MAP in general. The groups were similar in terms of oxygen saturation and $EtCO_2$ measurements. The results of our study are in line with the literature. The analysis of the data on $SatO_2$ and $EtCO_2$ measurements indicates that Ambu® AuraGain™ LMA provides sufficient ventilation to allow gas exchange in septoplasty.

None of our patients had soft tissue trauma, bleeding, hoarseness, or sore throat. Three patients in the ETT group developed nausea and 1 patient in the LMA group developed a cough. In their study on the complications of airway devices, Safaeian et al. [16] showed that the rate of complications was higher in the ETT group than in the LMA group. Lee et al. [7] compared the Ambu® AuraGain™ LMA with the I-gel™ (Intersurgical Ltd., Wokingham, England, second generation) LMA and found that complications were insignificantly less frequent in the Ambu® AuraGain™ LMA group.

In this study, airway pressure was always higher in the ETT group than in the LMA group. Endotracheal tube placement is longer and requires more manipulation. In addition, a laryngoscope is used as a helper tool for its insertion, which raises the risk of bronchospasm in these patients, and the tracheal tube causes a narrowing of the tracheal diameter.

Even a small bleeding in the operation area in the ear, nose, or throat affects the appearance of the operation area [17]. Although epinephrine is used to reduce pre-surgical bleeding, increases in arterial pressure can cause increase surgical bleeding [18]. In our study, MAP was generally low among patients in the LMA group. This low level contributes positively to the reduction of surgical bleeding.

Limitations

To avoid potential bias, precautions such as inclusion of similar patient groups in the study, not allowing repeated trials, and blind randomization were taken. However, visual evaluation could not be performed in our study since our hospital did not have fiberoptic equipment. Because this study was conducted on healthy adults, it may be misleading to use these data in children, and patients with systemic, hepatic, cardiac, and renal diseases. Although it is applied to all patients, the amount and concentration of epinephrine administered to the nasal area to provide a more comfortable space can also affect the hemodynamic data and the amount of bleeding.

Conclusion

We obtained similar results to tracheal intubation in terms of hemodynamic and respiratory parameters when Ambu® AuraGain™ LMA is used in septoplasty operations. Therefore, we think that Ambu® AuraGain™ LMA can be an alternative to tracheal intubation in septoplasty, and that our study may be a reference for future studies. However, it is an undeniable fact that more work is needed on this subject.

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Research article

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Comparison of clinical and laboratory parameters in patients with migraine or tension-type headaches: A case-control study

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The study was approved by the Clinical Research Ethics Committee of Bolu Abant Izzet Baysal University (Decision No: 2020/224, Date: 13.10.2020).
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Abstract

Background/Aim: Migraine and tension-type headaches (TTH) are common headache disorders that are not caused by or attributed to another disorder, and it is important to elucidate the clinical and laboratory features in patients with these diseases. This study aimed to compare the clinical and laboratory features of migraine patients with TTH.

Methods: Nineteen patients with TTH, 73 patients with migraine, and 30 volunteers without headache who visited Bolu Abant Izzet Baysal Training and Research Hospital between January 2018 and December 2018 were included in this case-control study. Patients' Fazekas score, age, gender, muscle score, hemogram parameters, parathyroid hormone, protein C, Protein S, Antithrombin III, low-density lipoprotein cholesterol, vitamin D, folate, vitamin B12 levels, antiphospholipid, anticardiolipin, thyroid autoantibodies, and ANA positivity were noted.

Results: The mean age in the migraine, TTH, and control groups were 43.54 (11.60), 47.05 (12.09), and 47.23 (12.33) years, respectively (P=0.261). There was no difference between the groups in terms of gender distribution (P=0.115). The Fazekas scores of the migraine (1[0-3]) and TTH groups (1[0-3]) were higher than controls (0[0-2]) (P<0.001).

Conclusion: Considering the Fazekas scores and antithrombin III levels in clinical and laboratory evaluation will be useful in the diagnosis and differentiation of migraine and TTH.

Keywords: Hormones, Migraine, Tension-type headache

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Introduction

Migraine, which is quite common all over the world, presents with recurrent headaches due to neurovascular pathophysiology and often negatively affects life [1]. Tension-type headache (TTH) is estimated to be more common than migraine; however, it is usually a less severe condition [2]. According to the global burden of disease study, TTH ranked third and migraine ranked sixth among the most common diseases [3]. Migraine is one of the main causes of disability worldwide, especially because of its relatively higher frequency among young adults and middle-aged women. Globally, migraine and TTH are suggested to account for 6.5% of disabled years [3].

Migraine and TTH are headache disorders that are not caused by or attributed to another disorder. Migraine and TTH are primarily clinical diagnoses, and currently, there are no laboratory tests of serum and cerebrospinal fluid samples or imaging studies that can be utilized for the confirmation of the diagnosis of migraine or TTH. Generally, tests are used to exclude possible underlying causes of secondary headaches [4, 5]. However, reports show that some laboratory tests, especially those measuring neuropeptides, may be used as biomarkers in patients with chronic headaches [6]. Therefore, it is important to elucidate the clinical and laboratory features (and the possible relationships between the two) in patients with migraine and TTH, which are the most common types of chronic headaches.

This study aimed to compare the clinical and laboratory features of migraine and TTH.

Materials and methods

In this case-control study, patients with tension headache, migraine, and volunteers without headache (healthy controls) who visited Bolu Abant Izzet Baysal Training and Research Hospital between January 2018 and December 2018 were evaluated.

Patients

Nineteen patients with TTH, 73 patients with migraine, and 30 controls without headache were included. All migraine patients had auras. All patients with TTH were selected consecutively from patients diagnosed in the neurology department. Patients with any chronic disease, psychiatric or neurological disease, and individuals without patient files, and those with missing relevant data were excluded. Healthy volunteers comprised the control group.

Ethics

The Clinical Research Ethics Committee of Bolu Abant Izzet Baysal University (Decision No: 2020/224, Date: 13.10.2020) approved the study. All principals in the Helsinki Declaration and Good Clinical Practice Guideline were followed during the study.

Measurements

The diagnoses of the patients were made in the Neurology Clinic according to international guidelines. In addition to the demographic characteristics of the patients, we determined and recorded Fazekas scores, hemogram parameters, parathyroid hormone (PTH), protein C, Protein S, Antithrombin III, low-density lipoprotein cholesterol (LDL), vitamin D, folate, vitamin B12 levels, ANA positivity, ENA profile, and antiphospholipid, anticardiolipin, thyroid autoantibody levels.

Evaluation of the Fazekas score

Two experienced neuroradiologists evaluated the White matter hyperintensity (WMH) independently from patients' imaging files via the semi-quantitative Fazekas scale. The Fazekas scale grades WMH on a four-point scale as follows: 0 points: None, 1 point: Dotted foci in the periventricular area, 2 points: Spread to periventricular halo or deep white matter, 3 points: Extension of periventricular WMH into the deep white matter [7].

Statistical analysis

PASS 11 program was used to calculate the sample size. Using the biochemical data gathered from the study conducted by Sarıcam [8], with 0.80 power and 0.05 alpha error, a minimum of 47 patients were required in each group.

SPSS v20 program was used for the data analysis. A normality check was performed using the Shapiro-Wilk test. In the expression of continuous data, we used median, lowest, and highest (min-max), or mean (standard deviation) values according to distribution. The Kruskal Wallis test or ANOVA was used to compare continuous data according to distribution. A pairwise comparison was performed using the Bonferroni test. Categorical data were compared using the Pearson Chi-Square test. *P*-value <0.05 value was considered significant.

Results

Ninety-four (77.0%) patients in the study groups were female, 28 (23.0%) were male and the mean age was 45.0 (11.8) years. Migraine, TTH, and control groups were similar in terms of age and gender distribution. The median Fazekas scores of the migraine and TTH groups were higher compared to the control group (P<0.001).

The antithrombin III values of the TTH group were significantly higher when compared to the other groups (P=0.011). Other parameters, including ENA profile, antiphospholipid, anticardiolipin, thyroid autoantibodies, and ANA positivity were similar between the groups (Table 1).

Table 1: Comparison of some features of migraine, TTH and the control group

	Control group	Migraine group	TTH group	*P*-value
Age (year) mean (SD)	47.2 (12.3)	43.5 (11.6)	47.0 (12.0)	0.261*
Gender, n (%)				
Female	19 (20.2%)	59 (62.8%)	16 (17.0%)	0.115^{x}
Male	11 (39.3%)	14 (50.0%)	3 (10.7%)	
Fazekas score, median (min-max)	0 (0-2)	1 (0-3)	1 (0-3)	<0.001
CRP	1.5(0-6.1)	1.1 (0-36.6)	1.3 (0-6.13)	0.638$^{\beta}$
WBC (×10^3 µl)	5.7 (3.4-12.0)	6.2 (3.3-10.3)	6.2 (3.3-12.6)	0.517$^{\beta}$
Neutrophil (×10^3 µl)	3.5 (1.6-8.0)	3.5 (1.3-7.7)	3.7 (1.5-8.7)	0.919$^{\beta}$
Lymphocyte (×10^3 µl)	1.9 (0.6-3.1)	2.0 (0.1-55.2)	1.9 (0.8-3.0)	0.684$^{\beta}$
Hemoglobin (g/dl)	14.0 (10.2-17.4)	13.6 (10.1-17.8)	14.3 (11.8-185)	0.132$^{\beta}$
Hematocrit (%)	41.7 (31.9-52.2)	40.3 (32.5-49.9)	41.6 (36.5-48.1)	0.116$^{\beta}$
MCV (fL)	87 (67-93)	86 (62-96)	86 (75-108)	0.764$^{\beta}$
RDW (%)	15.8 (14.7-19.2)	15.4 (12.8-82.7)	15.2 (12.9-17.0)	0.061$^{\beta}$
Platelet (×10^3 µl)	243 (116-362)	252 (16-433)	252 (144-404)	0.674$^{\beta}$
MPV (fL)	8.0 (5.8-10.9)	8.1 (4.9-18.9)	7.7 (6.0-11.2)	0.523$^{\beta}$
PDW (%)	17.6 (15.6-21.2)	17.3 (9.2-21.3)	17.5 (16.2-20.0)	0.242$^{\beta}$
Homocysteine (mmol /L)	12.9 (4.9-25.1)	11.6 (0-33.8)	12.5 (6.5-15.3)	0.837$^{\beta}$
Protein C (µg/mL)	114 (26-151)	98 (55-182)	102 (43-145)	0.150$^{\beta}$
Protein S (µg/mL)	88 (28-173)	85 (9-134)	75 (48-121)	0.436$^{\beta}$
Antithrombin III (µg/mL)	100 (79-133)	100 (74-138)	109 (100-137)	0.011$^{\beta}$
LDL (mg/dl)	121 (48-199)	121 (11-223)	134 (52-178)	0.433$^{\beta}$
PTH (pg/mL)	62 (10-192)	61 (0-125)	68 (33-142)	0.565$^{\beta}$
Vitamin D (ng/mL)	15.0 (5.6-52.3)	10.2 (1.5-112.6)	13.3 (5.8-42.8)	0.062$^{\beta}$
Folate (ng/mL)	7.9 (2.3-17.4)	6.8 (0-16.3)	7.8 (4.0-10.5)	0.787$^{\beta}$
Vitamin B12 (pg/mL)	288 (151-2000)	317 (135-1383)	335 (208-1588)	0.244$^{\beta}$

x: Chi-square test, * ANOVA test, $^{\beta}$ Kruskal Wallis test, CRP: C-reactive protein, WBC: White blood cell, MCV: Mean corpuscular volume, RDW: Red Cell Distribution Width, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, LDL: Low density lipoprotein, PTH: Parathormone

Discussion

In our study, patients with migraine and TTH and those without headaches were compared in terms of laboratory results. The median Fazekas scores of the migraine and TTH groups were higher compared to the control group, but the distribution of Fazekas scores between migraine patients and those with TTH did not differ significantly.

The Fazekas score is a scoring system that is generally used to evaluate changes in white matter in the examination of cerebrovascular events, and it can be measured via both magnetic resonance imaging and computed tomography [7, 9]. Studies with Fazekas scoring mostly focused on patients with migraines, and it has been shown that white matter changes are greater in these patients when compared to healthy controls without headaches [10-13]. Furthermore, in the few studies in which patients with TTH were evaluated, it has been reported that TTH also causes WMH [14]. For instance, in a study comparing the Fazekas scores of 4 groups (controls, migraine, TTH, and unclassified headaches), patients with TTH had more intense WMH relative to the control group. Interestingly, the study did not report any significant difference in terms of WMH when controls were compared with patients with migraines or unclassified headaches [14]. Conversely, in our study, it was found that the Fazekas scores of both the TTH and migraine groups were significantly higher compared to controls. In this context, we believe that it will be important to include both TTH and migraine groups in future WMH studies. This is especially important since most laboratory tests compared in this study were similar among the groups.

In a study evaluating hematological parameters in patients with migraines, no significant difference was found in WBC, MPV, and platelet counts [8]. Ulusoy et al. [15] reported that MPV values were higher in migraine patients compared to those with TTH and those without headaches. Similarly, some previous studies suggested impairment in platelet functions in the presence of various types of headaches [16, 17]. However, in our study, platelet counts and MPV values were similar in all three groups. Although previous studies suggested that migraine patients and individuals without headaches were similar in terms of platelet count and MPV, some other inflammation markers, such as CRP, were relatively increased when compared to controls [8]. Since the CRP value was not studied in our study, a comparison could not be made in this respect, but the groups were similar in terms of white blood cell count. There is a need for comprehensive studies assessing whether systemic inflammation is triggered during attacks or attack-free periods and whether there are differences in platelet count or MPV levels in migraine patients.

In our study, there was a significant difference between the groups in terms of antithrombin III level, which was higher in the TTH group compared to the other groups. Since some studies reported that headaches may occur due to thrombosis secondary to antithrombin III deficiency [18, 19], future studies may benefit from assessing this particular parameter in migraine patients with migraine or TTH.

Limitations

The main limitations include the retrospective nature of the study, the inability to control all confounding factors and exclusionary criteria, and the relatively small sample size. Additionally, migraine and TTH patients in this study were treated in a tertiary medical center; therefore, the patient group may have been biased towards a population with relatively severe disease.

Conclusions

Considering the Fazekas scores and antithrombin III levels in clinical and laboratory evaluation will be useful in the diagnosis and differentiation of migraine and TTH. Conducting comprehensive studies evaluating the laboratory parameters of migraine and TTH patients will be useful in elucidating conflicting results.

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The importance of mean platelet volume to lymphocyte ratio in predicting atrial fibrillation after coronary bypass operations

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Ethics Committee Approval
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Abstract

Background/Aim: The rate of postoperative atrial fibrillation (PoAF) after coronary artery bypass graft (CABG) operations ranges between 25-40%. Inflammation plays an important role in the pathogenesis of PoAF, and mean platelet volume and lymphocyte count are important inflammatory parameters. This study aimed to investigate the importance of the mean platelet to lymphocyte ratio (MPVLR) in predicting PoAF after CABG operations.

Methods: Three hundred and eighty consecutive patients who underwent on-pump CABG in our clinic between August 2016 and August 2020 were included in this retrospective observational cohort study. Patients with a known history of atrial fibrillation, reoperations, emergency operations, patients who had acute coronary syndrome within the last month, combined surgeries, those with systemic inflammatory disease, chronic autoimmune disease, chronic liver/kidney disease, and hematological diseases, and patients under steroid therapy were excluded from the study. Patients who did not develop postoperative PoAF were included in Group 1, while those who did were included in Group 2.

Results: There were 319 patients in Group 1 with a median age of 59 (32-83) years, and 61 patients in Group 2, with a median age of 66 (38-86) years (P<0.001). There was no difference between the groups in terms of gender distribution, hypertension (HT), diabetes mellitus (DM), smoking, body mass index, hyperlipidemia, ejection fraction, and current medical treatments (such as Angiotensin-converting enzyme inhibitor and beta-blocker therapy). The rate of chronic obstructive pulmonary disease (P=0.017), as well as MPV, MPVLR, intensive care unit stay and total hospitalization times were significantly higher (P<0.001 for all) in Group 2, while lymphocyte levels were significantly lower (P=0.006). Based on multivariate analysis, being over 70 years old (OR: 2.432, CI 95%: 1.966-3.723, P<0.001), having an ejection fraction below 35% (OR: 1.325, CI 95%: 1.190-1.1894, P=0.021) and MPVLR (OR: 1.821, 95%CI: 1.645-2.1592, P<0.001) were independent predictors of PoAF.

Conclusion: We found that the preoperative MPVLR value, which can be obtained from a simple hemogram test, is an important predictor of PoAF in patients who underwent CABG. MPVLR value can be a marker in determining risky groups preoperatively.

Keywords: Inflammation, Platelets, Coronary artery disease, Coronary artery bypass grafting, Postoperative term

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Introduction

Although endovascular procedures have come to the fore with the developing technology today, coronary artery bypass graft (CABG) surgery is still the most important treatment method for coronary artery disease (CAD) [1]. These technological advances have also improved cardiopulmonary bypass (CPB) systems, and CABG operations can be performed with low mortality and morbidity rates. However, apart from mortality, morbid conditions such as renal failure, atrial fibrillation, and cerebrovascular accident may occur after these operations [2-4]. Postoperative atrial fibrillation (PoAF), one of these cases, can be seen at a rate of 25-40%. This prolongs hospitalizations, increases treatment costs, and may lead to workforce loss [3, 4].

Inflammation not only plays a role in the pathogenesis of cardiovascular diseases, but also affects their progression. Many hemogram and routine biochemical parameters were used to predict prognosis after CABG operations because they are inexpensive and easily available [5, 6]. The most important of these parameters are related to lymphocyte count and mean platelet volume (MPV). In a recent study, preoperative high MPV value was an independent predictor of PoAF after CABG operations [7]. Preoperative low lymphocyte counts were also associated with PoAF in several studies [8]. In the light of all this information, mean platelet to lymphocyte ratio (MPVLR) seems a valuable prognostic marker in predicting PoAF.

This study aimed to investigate the importance of MPVLR in predicting postoperative atrial fibrillation after CABG operations performed with CPB.

Materials and methods

Patients who underwent CPB-guided isolated coronary bypass between January 2016 and January 2020 were included in this retrospective observational cohort study. The study was initiated after approval was granted by the ethics committee of Health Sciences University Bursa Yuksek Ihtisas Training and Research Hospital (2011-KAEK-25-2021/02-19). Demographic data of the patients (age, gender, chronic disease conditions such as hypertension, diabetes mellitus, etc.), preoperative blood parameters (hematocrit, white blood cell, neutrophil, lymphocyte, platelet count, MPV), operative data (perfusion times), and postoperative data (hospital and intensive care unit length of stay, drainage amounts, etc.) were obtained from the hospital registry. Patients with a known history of atrial fibrillation, reoperations, emergency operations, patients who had acute coronary syndrome within the last month, combined surgeries, those under steroid therapy, those with chronic autoimmune diseases, systemic inflammatory diseases, chronic liver/kidney diseases, and hematological diseases were excluded from the study. The implementation of these criteria left 380 consecutive patients to be included in the study. The primary endpoint of the study was the development of in-hospital PoAF after the operation. Patients who did not develop postoperative PoAF were included in Group 1, and those who did, made up Group 2.

Blood parameter analysis

All blood samples were obtained from peripheral venous structures during hospitalization. Hemogram (Beckmann Coulter LH 780) and biochemical (Cobas 6000, Manheim) measurements were performed using automatic analyzers. The MPVLR value was calculated as follows:

MPVLR= Mean platelet volume (fl) / lymphocyte count $10^3/\mu L$

Surgical technique

All patients underwent CABG with median sternotomy and standard CPB. All operations were performed by the same surgical team. Following the induction of anesthesia, a cardioplegic arrest was achieved after median sternotomy followed by aorta-two stage venous cannulation. All operations were performed in mild hypothermia (32 degrees Celsius). First, distal anastomoses were performed after aortic cross-clamping. When the distal anastomoses were done, the patient was warmed, and the heart was operated on by giving hot shot cardioplegia. Proximal anastomoses were performed with partial clamps. When sufficient hemodynamic status was obtained, the patient was weaned from the CPB, and the surgical incisions were closed. All patients were taken to the intensive care unit with close follow-up after the operation.

Postoperative Atrial Fibrillation Follow-up and Definition

Continuous electrocardiography (ECG) follow-ups were performed in all patients during their intensive care follow-up. Daily 12-lead ECG recordings were obtained from all patients followed up in the ward and the intensive care unit, as well as from those who had palpitation, sweating, and chest pain at the time of the complaint. PoAF was defined as the absence of P waves before QRS waves, and an irregular rhythm, lasting longer than five minutes.

Statistical analysis

SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) was used for data analysis. For continuous and ordinal data, mean and standard deviations were calculated using descriptive methods. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of distribution. For normally distributed data, the Student's t-test was used and the data were shown as mean (SD). The Mann-Whitney U test was used for non-normally distributed data, which were expressed as median (minimum-maximum). Frequency and percentile analyses were performed for the nominal data, which was compared with the Chi-Square test. Multivariate logistic regression analysis was used to assess the predictors of postoperative atrial fibrillation. A P value of less than 0.05 was considered statistically significant. Receiver-operating characteristic (ROC) curve analysis was performed for preoperative MPVLR to predict PoAF and the area under the curve was calculated.

Results

A total of 380 patients were included in the study, and the preoperative characteristics and demographic data of the patients are presented in Table 1. There were 319 patients in Group 1 with a median age of 59 (32-83) years, and 61 patients in Group 2, with a median age of 66 (38-86) years ($P<0.001$).

The groups were similar in terms of gender, hypertension (HT), diabetes mellitus (DM), smoking, body mass index, hyperlipidemia, ejection fraction, and current medical treatments (such as Angiotensin-converting enzyme inhibitor and beta-blocker therapy). The rate of chronic obstructive pulmonary disease was significantly higher in Group 2 (P= 0.017).

Table 1: Demographic data and preoperative features of the patients

Parameters	Group 1 (n=319)	Group 2 (n=61)	*P*-value
Age(years)	59 (32- 83)	66 (38-86)	<0.001
Female gender, n (%)	86 (26.9)	17(27.8)	0.879
COPD, n (%)	50 (15.6)	18 (29.5)	0.017
Hypertension, n (%)	186 (58.3)	38 (62.2)	0.518
Hyperlipidemia, n (%)	108 (33.8)	22 (36)	0.710
BMI (kg/m^2)	28.7 (23- 36)	29.3 (22.4-35.8)	0.226
Diabetes mellitus, n (%)	66 (20.6)	17 (27.8)	0.312
Smoking, n (%)	75 (23.5)	16 (26.2)	0.619
Beta blocker use, n (%)	140 (43.8)	23 (37.7)	0.412
ACEI/ ARB use, n (%)	161 (50.4)	28 (45.9)	0.541
EF (%)	50 (30- 65)	50 (25-65)	0.092
Left atrial diameter (cm)	3.5 (3.2- 4.4)	3.6 (3.3-4.8)	0.194

COPD: Chronic obstructive pulmonary disease, PCI: Percutaneous coronary intervention, CVA: Cerebrovascular accident, BMI: Body mass index, ACEI: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin receptor blocker, EF: Ejection fraction

Preoperative laboratory parameters and perioperative data of the patients are presented in Table 2. There was no difference between the groups in terms of white blood cell (WBC), hematocrit (Htc), platelet (PLT) count, neutrophil counts, urea, creatinine, C-reactive protein (CRP) values, drainage amounts, and perfusion times. In Group 2, MPV, MPVLR, intensive care, and total hospitalization times were significantly higher (for all parameters P<0.001), while lymphocyte levels were significantly lower (P=0.006).

Table 2: Preoperative laboratory variables and perioperative features of the patients

Variables	Group 1 (n=319)	Group 2 (n=61)	*P*-value ‡
White blood Cell (10^3/µL)	8.4 (4.5- 14.9)	8.7 (4.2- 14.3)	0.178
Hematocrit (%)	41.4 (33.6- 52.3)	40.2 (33- 51.5)	0.276
Platelet (10^3/µL)	252 (136- 496)	254 (130- 472)	0.189
MPV (fl)	8.4 (7.8- 10.2)	9.8 (8.9- 12.2)	<0.001
Neutrophil (10^3/µL)	4.4 (1.8- 8.8)	4.6 (2.2- 9.1)	0.094
Lymphocyte(10^3/µL)	2.3 (0.8- 4.4)	1.9 (0.7- 3.9)	0.006
Creatinine, mg/dL	0.99 (0.7- 2)	0.97 (0.8- 2)	0.494
Urea, mg/dL	20 (14- 40)	18 (16- 44)	0.256
C Reactive protein (mg/dL)	8.9 (0.6- 49.4)	9.2 (0.5- 44.9)	0.208
MPVLR	2.98 (2.61- 3.32)	4.71 (2.75- 6.48)	<0.001
Total perfusion time	90 (62- 196)	96 (55- 178)	0.128
Cross-clamp time	35 (21- 78)	38 (30- 75)	0.321
Total chest tube drainage (ml)	700 (200- 1600)	750 (300- 1500)	0.219
Total ICU stay (days)	2 (1- 9)	4 (2-16)	<0.001
Total hospital stay (days)	7 (5- 18)	111 (9- 28)	<0.001

‡ Mann Whitney U test, MPVLR: Meal platelet volume to lymphocyte ratio, TSH: Thyrotropin-stimulating hormone, T3: Triiodothyronine, T4: thyroxine.

Logistic regression analysis was performed to evaluate predictive parameters in predicting PoAF after CABG operations performed with cardiopulmonary bypass (Table 3). In univariate analysis, being over 70 years of age (odds ratio (OR): 3.945, confident interval (CI) 95%: 2.196-5.671, P<0.001), having an EF below 35% (OR:2.192, CI 95%:1.658-3.1690, P=0.005), COPD (OR: 0.889, CI 95%: 0.694-0.912, P=0.0020), low lymphocyte count (OR: 1.428 CI 95%: 1.212-1.894, P=0.008), MPV elevation (OR: 1.696, CI 95%: 1.422-1.987, P<0.001) and MPVLR elevation (OR: 2.874, CI 95%: 1.968-3.418 P<0.001) were significantly correlated with PoAF development. Based on multivariate analysis, being over 70 years old (OR: 2.432, CI 95%: 1.966-3.723, P<0.001), having an EF below 35% (OR: 1.325, CI 95%: 1.190-1.1894, P=0.021), and MPVLR elevation (OR:1.821, 95%CI: 1.645-2.1592, P<0.001) were independent predictors of PoAF.

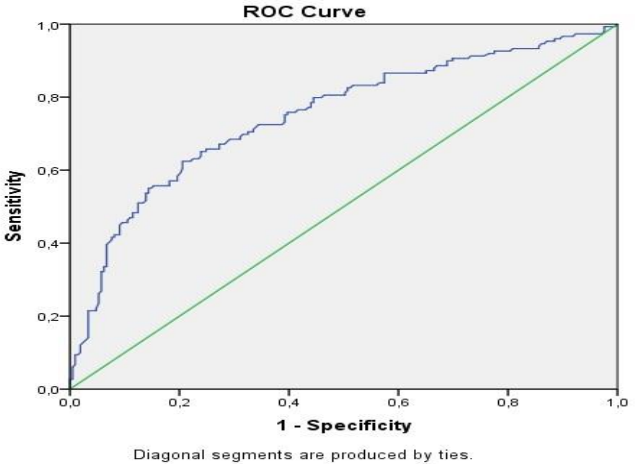
In the ROC curve analysis, the cut-off value for preoperative MPVLR was 4.96 (AUC: 0.749, P<0.001, 69.1% sensitivity, and 70.7% specificity) (Figure 1).

Table 3: Logistic regression analysis to identify factors affecting development of postoperative atrial fibrillation

Variables	Univariate analysis			Multivariate analysis		
	P-value	Exp(B) Odds Ratio	95% CI Lower - Upper	*P*-value	Exp(B) Odds Ratio	95% CI Lower - Upper
Age>70	<0.001	3.945	2.196-5.671	<0.001	2.432	1.966-3.723
EF<35	0.005	2.192	1.658-3.190	0.021	1.325	1.190-1.894
Hypertension	0.498	1.145	0.968-1.541	--	--	--
Diabetes Mellitus	0.298	0.786	0.696-1.110	--	--	--
COPD	0.020	0.889	0.694-0.912	0.246	1.114	0.965-1.237
Total perfusion time	0.130	1.022	0.954-1.326	--	--	--
Lymphocyte	0.008	1.428	1.212-1.894	--	--	--
MPV	<0.001	1.696	1.422-1.987	--	--	--
MPVLR	<0.001	2.874	1.968-3.418	<0.001	1.821	1.645-2.592

COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, MPV: Mean platelet volume, MPVLR: Mean platelet volume to lymphocyte ratio

Figure 1: ROC (Receiver operation characteristics) curve and AUC (Area under the curve) for mean platelet volume to lymphocyte ration (MPVLR) for predicting PoAF. (Cut off:4.96, AUC: 0.749, P<0.001, 69.1% sensitivity and 70.7% specificity)



Discussion

Today, coronary bypass operations can be performed with low mortality and morbidity. Postoperative atrial fibrillation is an important postoperative condition that prolongs hospitalizations and poses thromboembolic risks. The mechanism of PoAF formation depends on many factors and the reason for its occurrence is not fully understood [9]. Therefore, revealing the risk factors before the operation maintains its importance. This study investigated the predictive value of the relationship between platelet volume and lymphocyte count for PoAF, both of which are inflammatory parameters that can be obtained from simple hemogram values. In addition to known risk factors such as advanced age and low ejection fraction, we found that MPVLR value was an independent predictor of PoAF after CABG operations.

Inflammation plays a role in the pathogenesis of atherosclerotic coronary artery disease and may also affect the poor outcomes after CABG operations. PoAF is an important condition that can occur after CABG operations, and inflammation plays a vital role in its formation. Therefore, many inflammatory parameters have been investigated on this subject [8]. It is also important that an inflammatory parameter is as easily available as its predictive value. For this reason, the values that can be obtained from routine hemogram and biochemical parameters are important. MPV and NLR values are important

parameters in this respect. Platelets are important blood cells that play a role in the hemostatic process. It is known that platelet size is more effective for platelet functions than its numerical multiplicity. Large platelets contain denser granules and are more metabolically active [10, 11]. Accordingly, a high MPV value was reported as a risk factor for cardiac and cerebrovascular events [12]. Neutrophils play a prominent role in the inflammatory process because they secrete inflammatory parameters and lymphocytes regulate the inflammatory response [13]. NLR elevation, which occurs because of lymphocyte reduction, is used as an important inflammatory marker.

There are various studies in the literature investigating the effects of MPV values on PoAF. In a recent article by Cayır et al., the effect of MPV value on PoAF after CABG operations was investigated among 227 patients. PoAF was observed in 23.3% of the patients, and age, MPV, and total drainage amount were independent predictors of PoAF (OR=1.080, OR=1.371, OR=1.001; P=0.001, P<0.001, P=0.024, respectively) [7]. Erdem et al. investigated the relationship between MPV and PoAF in patients who underwent CABG, and 208 patients were included. Atrial fibrillation rate was 22%, and MPV, NLR, and CRP values were significantly higher in patients who developed atrial fibrillation (8.9 [1.4] vs. 7.9 [1.2], P<0.001, 3.2 1.9 etc. 2.6 1.2, P=0.005 and 8.9 [19.6] etc. 5.3 [8.7], P=0.025, respectively) [14]. In a recent study, MPV elevation was an independent predictor of PoAF (OR: 2.103, 95% CI: 1.324-3.339, P=0.002) in patients aged 65 years and over who underwent CABG [15]. In our study, MPV values were significantly associated with the development of PoAF.

Low lymphocyte count is an important indicator of general ill-health and physiological stress and constitutes a risk for atrial fibrillation in the general population [16, 17]. In a study by Erdolu et al. [5], low lymphocyte level was also a predictor of PoAF after off-pump CABG operations. A recent meta-analysis investigating the development of PoAF after cardiac surgery was published in mid-2020. As a result of a meta-analysis including 9,262 patients and 12 studies, the authors showed that the increase in NLR, which is also due to the preoperative low lymphocyte level, is associated with PoAF [18].

With all this literature information, MPVLR value seems an important parameter. The prognostic significance of MPVLR value in patients with diabetes mellitus who had acute myocardial infarction was investigated by Hudzik et al. [19]. The authors identified MPVLR as an independent risk factor for early and late mortality. In another study by Chen et al., the importance of MPVLR value in patients with acute ischemic stroke was investigated. MPVLR values at admission and 18-24 hours after intravenous thrombolysis, and the elevation of MPVLR at both times were predictors for poor outcomes [20]. In another recent study, high MPVLR values were associated with symptom development in patients with 50-79% carotid artery stenosis [21]. In our study, we determined the MPVLR value as an independent predictor for the development of PoAF, which is closely related to inflammation.

Being over 70 years old and having a left ventricular ejection fraction below 35% were other independent predictors of PoAF in our study. Advanced age not only causes the formation of many diseases but also affects their progression. With increasing age, fibrosis may occur in cardiac conduction pathways and atrial structures, which increases the risk of atrial fibrillation [22]. In addition, elderly patients may experience mobilization problems after cardiac operations, thus increasing the risk of PoAF [23]. In many studies, advanced age was associated with PoAF [3, 24]. Low ejection fraction also causes dilatation in the heart chambers of patients. Thus, changes occur in myocardial structures and conduction path problems increase. In one study, atrial fibrillation was found in 25% of patients with heart failure [25]. It is known to increase the risk of PoAF after cardiac surgery [5, 9, 22].

The most important limitations of our study include its single-center, retrospective nature and the small number of patients. In addition, due to the retrospective design of the study, continuous ECG monitoring could not be performed in the service follow-up of the patients. Atrial fibrillation episodes may have been missed in some patients who did not report any complaints in the service follow-ups.

Conclusion

Coronary bypass surgery is the most valuable treatment method for atherosclerotic heart disease. It is especially important to predict risky groups to increase the success rates of these operations. In this study, we determined that the preoperative MPVLR value, which can be obtained from a simple hemogram test, is an important predictor of PoAF in patients who underwent CABG. MPVLR values can be a marker in determining preoperative risk groups. Our study needs to be supported by multicenter prospective studies.

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Perceived stress level and health anxiety during COVID-19 pandemic period in patients with diabetes mellitus and hypertension: A prospective cross-sectional study

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Ethics Committee Approval
Ethics committee approval for this study was granted by Afyonkarahisar Health Sciences University Faculty of Medicine Ethics Committee (Number: 2020/506, date: 06.11.2020).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: Mortality rates of Coronavirus Disease 2019 (COVID-19) are increased in patients with chronic diseases such as diabetes mellitus (DM) and hypertension (HT). For this reason, some restrictions and lockdown measures were brought to these patients during the pandemic period, which may have disrupted their mental wellbeing. We aimed to investigate the relationship between the changes in the frequency of admissions of patients with DM, HT, DM+HT to the hospital during the pandemic and their perceived stress, health anxiety, general anxiety, and depression levels, and the change in stress burden experienced by disease type. This study intends to reveal the psychological problems that may develop due to the COVID-19 pandemic in DM, HT, and DM+HT patients and raise awareness.

Methods: DM, HT, and DM+HT patients admitted to Internal Medicine Outpatient Clinic between 01.12.2020-01.02.2021, and healthy volunteers who accepted to participate were included in this prospective cross-sectional study. Patients who did not match the age range, had additional comorbidities besides DM and HT, were treated for psychiatric disease, or were pregnant, and those who did not give consent were excluded. After a psychiatric interview was performed, the participants were asked to fill in the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Perceived Stress Scale (PSS), and Health Anxiety Scale (HAS). The effects of the COVID-19 pandemic on the frequency of admissions and perceived stress, health anxiety, general anxiety, and depression levels, and the change in stress burden experienced by disease type were examined.

Results: There was a significant difference in all scales used between the patient groups and the healthy control group (HAS $P<0.001$, BDI $P<0.001$, BAI $P=0.002$, PSS $P=0.001$). There was a significant decrease in the frequency of admission to the outpatient clinics among DM + HT patients ($P=0.002$). The mean duration of disease was lower in individuals whose frequency of admission to the outpatient clinic decreased ($P=0.006$). Patients with a family history of COVID-19 had significant decreases in the frequency of admission to the outpatient clinic ($P<0.001$) and had significantly disrupted medical treatment ($P=0.007$).

Conclusion: Patients with DM and HT, a short duration of chronic diseases, and history of COVID-19 infection in their families are more prone to be affected psychologically, and patients who are more psychologically affected refer less to the outpatient clinic. It is essential to continue treatment in consultation with psychiatry if DM and HT patients presenting to the outpatient clinic have one or more of these risk factors.

Keywords: COVID-19, Diabetes mellitus, Hypertension, Perceived stress level, Health anxiety

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Introduction

It is known that chronic diseases such as diabetes mellitus (DM) and hypertension (HT) are risk factors in Coronavirus Disease 2019 (COVID-19)-related mortality [1,2]. These individuals with chronic diseases should be more careful about social measures taken against the pandemic [3]. At first, in the People's Republic of China and later in many countries, curfews were imposed on those with chronic diseases for their protection from COVID-19 [4]. Lockdown and isolation are the leading measures taken to protect the public during a pandemic [5]. However, these measures taken to protect the physical health of individuals may seriously affect their mental health in the future [6]. Previous studies state that long-term lockdown measures during a pandemic cause increased anxiety, depression, and anger in individuals [7, 8].

Another problem encountered during the pandemic, apart from restrictions such as isolation, social distance rules, and curfew, is that individuals with chronic diseases cannot continue their routine health checks and treatments as before the pandemic period [9]. Doctors being assigned to COVID-19 units other than their areas of expertise, the rapid increase in the number of COVID-19 patients in hospitals, and the reluctance to use public transport due to the fear of COVID-19 transmission cause a decrease in the number of hospital admissions for individuals with chronic diseases. The decrease in the number of admissions may cause a delay in the routine controls of patients and their treatment and increase complications [10].

It is known that the individuals with chronic diseases such as DM and HT accessed the health centers less during the pandemic compared to the pre-pandemic period, and depression and anxiety increased in most individuals with chronic diseases [11-13]. However, no study investigated the relationship between the change in the frequency of outpatient visits and psychological symptoms.

Another factor affecting the frequency of referral to the outpatient clinic is health anxiety, which manifests as two different behavior types in individuals. First, the person may refuse to be admitted to the hospital due to increased health anxiety and fear of contamination. Second, because of their increasing health anxiety, they may refer to the hospital more often to get information from the doctor [14]. However, our literature review revealed that the health anxiety data of the individuals with chronic diseases during the pandemic were limited.

This prospective cross-sectional study aimed to investigate the relationship between the changes in the frequency of admissions of patients with DM, HT, DM+HT to the hospital during the pandemic and their perceived stress, health anxiety, general anxiety, and depression levels, and the change in stress burden experienced by disease type.

Materials and methods

Ethics statement

Ethics committee approval was granted by Afyonkarahisar Health Sciences University, Faculty of Medicine Ethics Committee (Number: 2020/506, date: 06.11.2020). The study was carried out following the Helsinki Declaration.

Research method and study population

Patients who visited the Internal Medicine Outpatient Clinic of AFSU Medical Faculty Hospital between 01.12.202-01.02.2021, were followed up and treated with the diagnosis of HT and/or DM and accepted to participate were included in this prospective cross-sectional study. Patients who did not match the age range, had other comorbidities besides DM and HT, were treated for psychiatric disease, were pregnant, and did not give voluntary consent were not included. A total of 160 volunteers, including 40 HT, 40 DM, 40 DM+HT patients, and 40 healthy controls were included in the study. After a psychiatric interview, the participants were asked to fill in the Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Perceived Stress Scale (PSS), and Health Anxiety Scale (HAS). One hundred sixty-seven volunteers were interviewed for inclusion in the study, but seven patients who expressed their reluctance to fill the scales were excluded. If any of the participants needed further psychiatric evaluation or initiation of treatment, feedback was given to the participant, and psychiatric follow-up was provided if the individual agreed.

The effects of the COVID-19 pandemic on the frequency of admissions and perceived stress, health anxiety, general anxiety, and depression levels, and the change in stress burden experienced by disease type were examined.

Assessment Tools

Sociodemographic form: It is a form established by the researchers to obtain information about the sociodemographic and clinical characteristics of the individuals participating in the study. The form contained information such as the individual's age, gender, education, marital status, employment status, duration of disease, and the change in the frequency of hospital admissions during the pandemic.

Survey form structured by researchers: The COVID-19 history of the participants was questioned, and if they had COVID-19, they were asked about their clinical presentations: Asymptomatic, mild (treated at home), moderate (hospitalized and treated), severe (treated in the intensive care unit). Besides, it was recorded whether the family members of the participants who lived together had a COVID-19 infection. The last two questions in the questionnaire form were "My medical treatment was interrupted due to the pandemic," and "A relative/family/friend of mine died due to COVID-19", with either “true” or “false” as answer choices.

Beck Depression Inventory: The Turkish validity and reliability study of this scale developed by Beck et al. [15] was conducted by Hisli [16]. It is a self-report scale consisting of 21 items on the cognitive, physical, and emotional symptoms seen in depression. The highest score that can be obtained is 63.

Beck Anxiety Inventory: It is a self-assessment scale developed by Beck et al. in 1988 to determine the frequency of anxiety symptoms experienced by the individuals [17]. It is a Likert-type 21-item scale scored between 0 and 3, and the total score ranges between 0 and 63. Its validity and reliability in Turkey were carried out by Ulusoy et al. [18].

Perceived Stress Scale: It is a scale developed by Cohen et al. [19] to evaluate how stressful the individual perceives the situations s/he encounters, and its Turkish adaptation was performed by Eskin et al [20]. This 5-point Likert

type scale indicates the person's stress level, and the 8-question form of the scale was used in our study. The total score ranges from 0 to 32.

Health Anxiety Scale: The first 14 items of the 18-item scale, developed by Salkovskis et al. [21], contain four sequential answers questioning the mental state of the patients, while the last four items question the mental state of the patients with the assumption that they have severe disease. The Turkish validity and reliability study was conducted by Aydemir et al [22]. The total score of the scale ranges from 0 to 54.

Statistical analysis

The data obtained were evaluated by the SPSS version 25 package program (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test revealed non-normally distributed data. Mann-Whitney U test was used for binary group comparisons in which significant differences between the groups were evaluated, and the Kruskal Wallis-H test was used for multiple group comparisons. Analysis results were presented as mean±standard deviation, median, minimum, and maximum values. While the Pearson chi-square test was used to determine the prevalence of categorical variables, outcome data were expressed with frequency and percentages. Spearman correlation test was used to evaluate the continuous relationship between variables. Results were evaluated at a 95% confidence interval, and a *P*-value of <0.05 was considered statistically significant. Power analysis was performed under the following conditions: Effect size: 0.25 (medium), α error: 0.05, power: 0.74, number of groups: 4, total sample size: 160.

Results

A total of 120 patients, including 40 HT patients, 40 DM patients and 40 DM + HT patients, and 40 healthy volunteers in the same age range were included in the study. The sociodemographic characteristics of the participants, the duration of chronic disease, medical treatment disruption, the history of COVID-19, and the change in the frequency of admission to the outpatient clinic are presented in Table 1.

The frequency of visits to the outpatient clinic of the DM+HT patient group decreased significantly compared to the other groups (*P*=0.002) and was associated with having a history of COVID-19 in one of the family members (*P*<0.001) and the disruption of the medical treatment (*P*=0.007). These differences indicated that patients with a history of COVID-19 in their family members visited the outpatient clinic less, and hence reported more disruptions in the medical treatment. Categorical data of the variables are presented in Table 2.

The mean duration of diseases of the individuals whose frequency of admission to the outpatient clinic decreased was significantly lower than the groups whose admission frequency did not change/increased (*P*=0.006). In addition, when the medians of the scales applied to the participants were evaluated, it was found that all the scales were higher in patients with a decreased frequency of referral to the outpatient clinic (HAS, PSS, BAI, BDI, *P*<0.001) (Table 3).

Table 1: The sociodemographic characteristics of the participants

		DM (n %)	HT (n %)	DM+HT (n %)	Healthy Control (n %)
Age (Mean (SD))		51 (12)	52 (11)	56 (9)	50 (12)
Gender	Female	23 (57.5%)	21 (52.5%)	22 (55%)	22 (55%)
	Male	17 (42.5%)	19 (47.5%)	18 (45%)	18 (45%)
Marital status	Single	6 (15%)	6 (15%)	5 (12.5%)	9 (22.5%)
	Married	34 (85%)	34 (85%)	35 (87.5%)	31 (77.5%)
Educational status	Lack of education	9 (22.5%)	5 (12.5%)	10 (25%)	2 (5%)
	0-5 years	10 (25%)	15 (37.5%)	18 (45%)	10 (25%)
	6-8 years	9 (22.5%)	7 (17.5%)	5 (12.5%)	5 (12.5%)
	9-12 years	5 (12.5%)	9 (22.5%)	3 (7.5%)	11 (27.5%)
	More than 13 years	7 (17.5%)	4 (10%)	4 (10%)	12 (30%)
Employment status	Employed	16 (40%)	14 (35%)	17 (42.5%)	23 (57.5%)
	Housewife	15 (37.5%)	17 (42.5%)	15 (37.5%)	14 (35%)
	Unemployed	3 (7.5%)	1 (2.5%)	2 (5%)	0 (0%)
	Retired	6 (15%)	8 (20%)	6 (15%)	3 (7.5%)
Frequency of outpatient clinic admission	Not changed	19 (47.5%)	31 (77.5%)	17 (42.5%)	-
	Decreased	16 (40%)	6 (15%)	22 (55%)	-
	Increased	5 (12.5%)	3 (7.5%)	1 (2.5%)	-
Duration of disease (month) (median/min-max)		48 (1-300)	60 (1-240)	78 (24-420)	
Medical treatment	Disrupted	8 (20%)	14(35%)	11 (27.5%)	-
	Not Disrupted	32 (80%)	26 (65%)	29 (72.5%)	-
COVID-19 history of individuals	Did not have	30 (75%)	31 (77.5%)	31 (77.5%)	27 (67.5%)
	Asymptomatic	0 (0%)	1 (2.5%)	0 (0%)	1 (2.5%)
	With mild symptoms	6 (15%)	6 (15%)	7 (17.5%)	11 (27.5%)
	With moderate symptoms	4 (10%)	2 (5%)	2 (5%)	1 (2.5%)
	With severe symptoms	0 (0%)	0 (0%)	0 (0%)	0 (0%)
A family member had COVID-19	Yes	22 (55%)	11 (27.5%)	17 (42.5%)	18 (45%)
	No	18 (45%)	29 (72.5%)	23 (57.5%)	22 (55%)
Family/Relative/ Friend you know died due to COVID-19	Yes	12 (30%)	12 (30%)	17 (42.5%)	24 (60%)
	No	28 (70%)	28 (70%)	23 (57.5%)	16 (40%)

DM: Diabetes Mellitus, HT: Hypertension

Table 2: Frequency of outpatient clinic admission

		Not changed (n %)	Decreased (n %)	Increased (n %)	*P*-value
Patient groups	DM	19 (47.5%)	16 (40%)	5 (12.5%)	0.002*
	HT	31 (77.5%)	6 (15%)	3 (7.5%)	
	DM+HT	17 (42.5%)	22 (55%)	1 (2.5%)	
A family member had COVID-19	Yes	14 (28%)	30 (60%)	6 (12%)	
	No	53 (75.71%)	14 (20%)	3 (4.29%)	<0.001**
Medical treatment	Disrupted	11 (33.33%)	20 (60.61%)	2 (6.06%)	0.007*
	Not Disrupted	56 (64.37%)	24 (27.59%)	7 (8.05%)	

DM: Diabetes Mellitus, HT: Hypertension, * *P*<0.05, There was a significant difference. ** *P*<0.001, There was a significant difference.

Table 3: Frequency of outpatient clinic admissions according to scales, age, and duration of disease

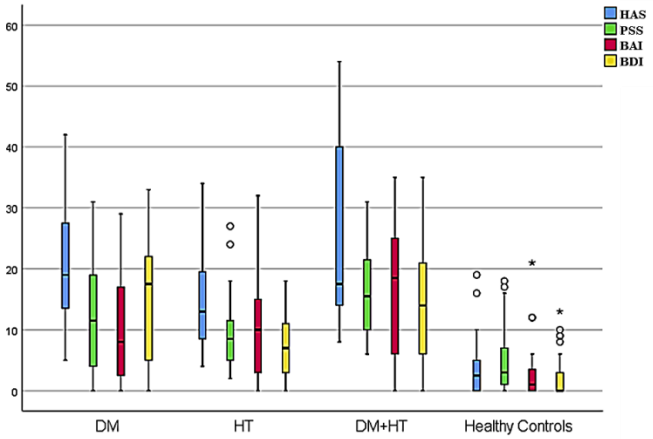
Parameters		Frequency of outpatient clinic admissions			*P*-value
		Not changed	Decreased	Increased	
Age	Mean (SD)	54.36 (11.31)	52.41 (10.40)	49.78 (7.03)	0.204
	Median	55	52.5	52	
	Min	23	27	39	
	Max	70	68	58	
Duration of disease (month)	Mean (SD)	113.01 (94.04)	61.2 (67.15)	92 (47.62)	0.006*
	Median	96	48	72	
	Min	1	1	48	
	Max	420	408	180	
HAS	Mean (SD)	13.58 (6.30)	31.09 (11.75)	19 (9.23)	<0.001**
	Median	13	33	18	
	Min	4	9	5	
	Max	30	54	36	
PSS	Mean (SD)	8.58 (4.81)	19.09 (6.73)	10.11 (8.96)	<0.001**
	Median	8	44336	8	
	Min	1	2	0	
	Max	27	31	24	
BAI	Mean (SD)	7.93 (8.18)	19.23 (8.33)	9.89 (6.58)	<0.001**
	Median	5	44335	10	
	Min	0	0	1	
	Max	32	35	18	
BDI	Mean (SD)	8.97 (6.91)	18.59 (8.93)	8.22 (6.90)	<0.001**
	Median	7	44334	5	
	Min	0	2	0	
	Max	27	35	19	

HAS: Health Anxiety Scale, PSS: Perceived Stress Scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, * *P*<0.05, There was a significant difference. ** *P*<0.001, There was a significant difference.

The change in the frequency of admission to the outpatient clinic was not affected by sociodemographic data such as age, gender, educational status, marital status, and the patient's history of COVID-19 (*P*=0.204, *P*=0.145, *P*=0.652, *P*=0.763, *P*=0.085, respectively). All scale scores significantly differed

between the patient groups and the healthy control group (HAS $P<0.001$, BDI $P<0.001$, BAI $P=0.002$, PSS $P=0.001$). The HAS and BDI values of the patients in the HT group were significantly lower than those of the DM and DM+HT groups ($P<0.05$). The BAI and PSS scores of the DM+HT group patients were significantly higher than those of DM and HT group patients ($P<0.05$). The medians of the scales applied to the participants were shown in Figure 1.

Figure 1: The scales used according to the patient groups and the healthy control group



DM: Diabetes Mellitus, HT: Hypertension, HAS: Health Anxiety Scale, PSS: Perceived Stress Scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory

All scale scores of those with a family history of COVID-19 were significantly higher than those without a history of COVID-19 (HAS $P=0.001$, BDI $P=0.006$, BAI $P=0.007$, PSS $P=0.004$). The relationship between scale scores, age, and duration of the disease is presented in Table 4.

Table 4. The correlation between scale scores applied to the participants and age, and duration of the disease

			Age (years)	Duration of illness (month)
DM	HAS	r	-0.450	-0.684
		P-value	0.004**	<0.001**
	PSS	r	-0.417	-0.537
		P-value	0.007**	<0.001**
	BAI	R	-0.439	-0.550
		P-value	0.005**	<0.001**
	BDI	r	-0.512	-0.542
		P-value	0.001**	<0.001**
HT	HAS	r	-0.197	-0.084
		P-value	0.223	0.604
	PSS	r	-0.189	-0.191
		P-value	0.244	0.238
	BAI	r	0.041	0.029
		P-value	0.803	0.860
	BDI	r	-0.064	-0.027
		P-value	0.696	0.867
DM+HT	HAS	r	-0.404	-0.731
		P-value	0.010**	<0.001**
	PSS	r	-0.227	-0.728
		P-value	0.158	<0.001**
	BAI	r	-0.328	-0.483
		P-value	0.039*	0.002**
	BDI	r	-0.268	-0.558
		P-value	0.094	<0.001**
Healthy Controls	HAS	r	0.369	-
		P-value	0.019*	
	PSS	r	0.202	
		P-value	0.211	
	BAI	r	0.100	
		P-value	0.539	
	BDI	r	-0.095	
		P-value	0.561	

DM: Diabetes Mellitus, HT: Hypertension, HAS: Health Anxiety Scale, PSS: Perceived Stress Scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, *The correlation is significant at 0.05. ** The correlation is significant at 0.001.

Discussion

While lockdown and isolation measures are taken to protect the physical health of individuals from infectious diseases during the pandemic, the mental health of those who experience such restrictions should also be taken into account. Individuals with chronic diseases may be worried that their disease will progress more severely in the event of an infection. On the other hand, they may bear the burden of being stigmatized by society [23]. Stigmatized communities are known to tend to hide their disease or seek medical help late [24]. Due to underlying psychodynamic factors, the pandemic may cause an increase in psychological burden by preventing individuals with chronic diseases from accessing health care and medical treatment [25]. In this context, our study evaluated whether the mental state of the patients varied with their chronic diseases. All scale scores were higher in the DM+HT group, which had the highest psychological risk. The decrease in the frequency of admission to the outpatient clinic was more pronounced in DM+HT patients, which indicates that DM+HT patients were the most sensitive. Diversely, individuals with DM disease alone had higher health anxiety and depression scale scores than DM+HT patients and adding HT to DM increased the perceived stress and anxiety. The scale scores of the HT patient group were higher than the healthy control group, but their health anxiety and depression scores were lower than those of the DM and DM+HT patients. These results are in line with the literature, and individuals with chronic diseases are more prone to be psychologically affected during the pandemic [11-13].

The duration of disease was a critical variable, especially in DM and DM+HT patients, and the scale scores showed a strong inverse correlation with the duration of the disease. In other words, as the disease became chronic in these patients, the individual showed fewer psychological symptoms. Also, patients whose frequency of admission to the outpatient clinic decreased had a lower duration of disease. These data show that individuals whose admission to the outpatient clinic decreased needed more psychological support.

Studies investigating the psychosocial status of individuals with chronic diseases during the COVID-19 pandemic process were examined in the literature [26-30]. Louvardi et al. [26] revealed that the anxiety and depression levels of individuals with chronic diseases were no different from the healthy control group. In other studies conducted during the pandemic period, individuals with chronic diseases had higher levels of depression, anxiety, and stress, and especially young chronic patients were affected more [27-28]. Supporting the findings of Ozamiz-Etxebarria et al. [27] and Sayeed et al. [28], we observed that the perceived stress, health anxiety, depression, and anxiety levels of individuals with chronic diseases were higher than the healthy group. Contrary to the study conducted by Bergman et al. [29], which suggests that elderly individuals experience more health anxiety during the pandemic process and supporting that conducted by Ozamiz-Etxebarria et al. [27], we found that perceived stress, health anxiety, and depression levels were inversely correlated with patient age and disease duration. However, the study by Bergman et al. [29] was conducted on the general population, not on sick individuals, and our control group data were consistent with their results.

Health anxiety is not affected by the person's age but by the presence of chronic diseases. While health anxiety increases with age in individuals without chronic diseases, the contrary is

observed in individuals with chronic diseases. This result is consistent with the information suggested by Demiray et al. [30] that as the age of the patient increases, the level of threat perception decreases. All scale scores showed an inverse correlation with age and disease duration, especially in DM patients, but not in HT patients. Although the health anxiety and general anxiety levels decrease with age in DM+HT patients, it is noteworthy that the perceived stress and depression do not vary with age but are inversely correlated with the duration of the disease. This relationship shows us that the perceived stress and depression decrease as the duration of the disease increases in DM+HT coexistence, but this is not related to age. Therefore, the prolongation of the disease duration is a more critical variable than age.

In the literature, it was reported that having COVID-19, having a relative with COVID-19, or losing someone close to COVID-19 cause an increase in stress, depression, and anxiety [31]. We determined that one of the family members having had COVID-19 increased the perceived stress, health anxiety, general anxiety, and depression levels in DM patients. In the DM+HT group, while perceived stress increases the level of health anxiety and general anxiety, it does not affect depression levels. In the HT patient group, having a family member who had COVID-19 did not affect the scale scores. We attribute this to the lower health anxiety of the HT group compared to the other patient groups.

However, the reason for the increase in psychological scales in patients with a history of COVID-19 infection in their families is that the psychological burden increases as the threat approaches. The fact that a similar relationship was not observed in healthy controls made us think that chronic disease affected the psychological burden.

Our study revealed that the individual having had COVID-19 or lost an acquaintance because of COVID-19 did not affect the scale scores. This is thought to be due to the low rate of COVID-19 among the volunteers who agreed to participate in the study (29.12%) and the fact that patients who participated in the study and had COVID-19 in their history often consisted of patients with mild infection.

Contrary to the study of Chudasama et al. [11] emphasizing that the use of health services by COVID-19 decreased more in patients with HT than in DM patients, in the present study, the decrease in the frequency of admission to the outpatient clinic was highest in the DM+HT group, and the HT group reported the smallest decrease. The reason for this difference is that Chudasama et al.'s study was online, and a survey study was conducted on the notification of healthcare workers, while our study was based on information obtained directly from the outpatients.

It is striking that the duration of the patients' disease whose number of outpatient clinic admissions decreased in our study was shorter. Besides, considering that individuals with a short duration of the disease have higher scale scores, it is seen that patients with a shorter disease duration are more psychologically sensitive and try to protect themselves by avoiding hospital admissions. Therefore, we think that patients with a short duration of the disease need more psychological support. One of the strengths of our study is that no study in the literature accommodates the duration of disease with scale scores. 72.5% of the patients participating in our study stated that they did not have any problem accessing medical treatment. We think that this is since, within the framework of the measures taken in our country, the duration of drug reporting is extended, and the drugs can be purchased directly from the pharmacy without admitting to the health facility. Ease of access to medical treatment may be another determinant of the decrease in the frequency of referral to the outpatient clinic [32].

Although patients do not have any problems in accessing medical treatment, a significant decrease in the number of referrals to the outpatient clinic will delay the routine control examinations and increase the complications associated with chronic disease [10]. It is known that patients with depression or anxiety as a comorbidity to chronic disease have a more severe course of the disease and more symptoms than those with chronic disease alone [33-35]. It is noteworthy that 36.6% of our patients with these two chronic diseases, which are thought to affect a large part of the population in our country, stated that their frequency of referring to the outpatient clinic decreased. This may cause difficulties in the follow-up of the chronic disease while trying to be protected from the pandemic. In this context, determining the priority group among chronic patients during a pandemic is essential for disease management. Because the responsibility of chronic illness will lead to an increase in the individual's health anxiety and perceived stress, disease management becomes difficult as well as the social perceived stress. It is crucial to enlighten the subject with the proposed cohort studies to be conducted in the future.

Limitations

The results obtained from the study are limited because of the cross-sectional nature of the study. Also, the COVID-19 pandemic began in March 2020 in our country. Most authors (who planned the study) worked in the COVID-19 intensive care unit until the end of October 2020, and ethics committee approval was obtained in November 2020. There was a reduction in the number of patients with chronic diseases who visited the hospital during the COVID-19 pandemic.

Conclusion

During the pandemic, individuals with chronic diseases had higher levels of health anxiety, perceived stress, general anxiety, and depression compared to healthy individuals. The stress and general anxiety levels perceived by HT and DM patients during the COVID-19 pandemic were similar. However, DM+HT patients had higher perceived stress and general anxiety levels. While the level of health anxiety and depression was similar in DM and DM+HT groups, it was lower in the HT group. Patients with a short duration of disease and history of COVID-19 infection in their families were more prone to be affected psychologically, and more affected patients referred to the outpatient clinic less frequently. It is essential to continue treatment in consultation with psychiatry if patients presenting to the outpatient clinic have one or more of these risk factors.

To prevent more severe consequences in the future, it is recommended to prioritize measures such as increasing telemedicine services, providing online consultancy services, increasing virtual platforms that can provide synchronous-asynchronous health services, determining the regional health

facilities with the lowest risk of infection, and continuing routine disease screenings.

During the pandemic process, it is essential to increase mental health and physical health measures for individuals with chronic diseases and identify high-risk individuals.

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Evaluation of colonoscopy results of patients in a colorectal cancer screening program: A retrospective cohort study

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The study was approved by the local Ethics Committee of the University of Health Sciences, Tepecik Training and Research Hospital (approval number: 2020/14-55, approval date: 23.12.2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Colorectal cancer is at the forefront of cancer-related deaths. Early detection and treatment of precursor lesions with screening programs are imperative. In this study, we aimed to determine the outcomes of colonoscopy and the effectiveness of screening.

Methods: The colonoscopy results of 758 patients who were referred for positive fecal occult blood tests between October 2015 and January 2020 were examined in this retrospective cohort study. The demographic, pathological, and colonoscopic findings were recorded.

Results: No pathology was detected in 53.3% of patients during colonoscopy. In patients with a pathology, polyps (28.5%), diverticular disease (15.44%), and colitis (2.37%) were most common. Patients with malignancy accounted for 3.69% of all patients and 12.96% of patients with polyps. Among adenoma types, the risk of dysplasia and/or malignancy was higher in villous polyps compared to tubulovillous and tubular polyps, and in tubulovillous polyps compared to tubular polyps ($P<0.01$). The presence of dysplasia and/or malignancy was evaluated mutually between the subgroups according to polyp size. There was no significant difference in the incidence of dysplasia between the patients with polyps of 6-10 mm and those with polyps of 11-20 mm ($P=0.192$). Among all other subgroups, an increase in polyp size caused a significant increase in dysplasia and/or malignancy ($P<0.001$).

Conclusion: The results of this study showed that colonoscopy performed on colorectal cancer screening patients with a positive fecal occult blood test was quite successful in diagnosing precancerous lesions and colorectal cancer.

Keywords: Colorectal cancer, Screening, Polyps, Malignancy

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Introduction

Colorectal cancer (CRC) is the fourth most diagnosed and third most fatal cancer worldwide, according to World Health Organization GLOBOCAN 2018 data. It accounts for 11% of all cancer diagnoses [1]. Detection of precancerous lesions and early-stage cancers is important for CRC. Given the normal mucosa-adenoma-cancer sequence, detection of adenomas and attempts to address them are becoming important, especially among the screening population [2]. For this reason, CRC can be easily overlooked; however, it is preventable if appropriate screening methods are used [3]. Screening for colorectal cancer is conducted to screen a population at risk without any symptoms for asymptomatic precancerous lesions and early-stage tumors [4]. The program, which has been successfully managed since 2015 under the leadership of the Ministry of Health in our country, is carried out in Cancer Early Detection and Screening Center and Family Health Centers, and colonoscopy centers. In this study, we aimed to determine the effectiveness of the colonoscopy results and screening of patients aged between 50-70 years who were referred to the general surgery outpatient clinic due to the positive fecal occult blood (FOB) tests performed at first-line health institutions.

Materials and methods

The data of patients who were referred to our hospital's general surgery outpatient clinic between October 2015 and January 2020 because of positive FOB tests conducted in first-line medical institutions and underwent colonoscopy were reviewed in this retrospective cohort study. The age, gender, whether polyps were detected, the procedure used in patients with polyps, surgery, and pathology results after the diagnosis of malignancy were evaluated in patients with complete colon cleansing whose cecum could be reached in colonoscopy. Patients whose cecum could not be reached due to insufficient colon-cleansing, patient intolerance and anatomical reasons were excluded from the study.

Statistical analysis

The Statistical Package for Social Sciences (SPSS for Windows v.25.0) was used for statistical analyses. Descriptive statistics involved mean and standard deviation. Crosstables were shown as percentage ratios. The continuous data were examined in terms of distribution with the Shapiro-Wilk test. Then, the data were statistically compared using the unpaired t-test for normally distributed samples or the Mann-Whitney U test for non-normally distributed samples. Variables with categorical data were compared using chi-square or Fisher's exact tests. Analysis of Variance (ANOVA) was used to compare the groups. A post hoc Games-Howell multiple comparison tests was utilized to compare the subgroups. The statistical significance level was $P<0.05$.

Results

Colonoscopies were performed on 758 patients, 369 females, and 389 males, all of whom were admitted due to FOB positivity during the screening period. The median age was 59.5 years (min 47 - max 77). No pathologies were detected in the colonoscopy of 405 patients. The most common pathologies included polyps, diverticular disease, and colitis, in order of frequency. One patient was diagnosed with a solitary rectal ulcer, and one was diagnosed with melanosis coli. Demography and colonoscopy data of patients are presented in Table 1.

The number of patients with polyps was 216 (28.5%). Among them, 133 (61.57%) were male and 83 (38.43%) were female. The median age was 60.29 (±6.05) years. One hundred twenty-three patients (56.94%) underwent polypectomy. Tubular adenoma was most observed, while a low-grade neuroendocrine tumor was reported in 1 patient. High-grade dysplasia was detected in 19 patients, and 28 malignancies were observed, 5 of which were intramucosal carcinoma and 23 of which were adenocarcinoma. Patients with malignancy accounted for 3.69% of all patients and 12.96% of patients with polyps. A follow-up decision was made for 3 of 28 patients diagnosed with malignancies and for a NET-diagnosed patient. Demography, pathology, and colonoscopy data of patients with polyps are shown in Table 2.

Table 1: Demographic and colonoscopic findings of all colorectal cancer screening patients

		n	%
Sex, n %	Female	369	48.68
	Male	389	51.32
Age, median, min-max		59.5	47-77
Colonoscopic findings, n %	Normal	405	53.43
	Polyp + Mass	216	28.50
	Diverticular disease	117	15.44
	Colitis	18	2.37
	Solitary rectal ulcer	1	0.13
	Melanosis coli	1	0.13

min: minimum, max: maximum

Table 2: Demographic, colonoscopic and pathological characteristics of colorectal cancer screening patients with polyps (n=216)

		n	%
Sex, n %	Female	83	38.43
	Male	133	61.57
Age, mean (SD)		60.29 (6.05)	
Localization, n %	Rectum	37	17.13
	Sigmoid Colon	114	52.78
	Descending Colon	17	7.87
	Splenic Flexure	3	1.39
	Transverse Colon	26	12.04
	Hepatic Flexure	5	2.31
	Ascending Colon	7	3.24
	Cecum	7	3.24
Polyp size, n %	<5 mm	77	35.65
	6-10 mm	76	35.19
	11-20 mm	40	18.52
	>20 mm	23	10.65
Action, n %	Polypectomy	123	56.94
	Biopsy	93	43.06
Adenoma Type, n %	Tubular	123	56.94
	Tubulovillous	47	21.76
	Villous	25	11.57
	Hyperplastic polyp	16	7.41
	Inflammatory polyp	4	1.85
	NET	1	0.46
Dysplasia, n %	None	83	38.43
	Low-grade	86	39.81
	High-grade	19	8.80
	Intramucosal carcinoma	5	2.31
	Adenocarcinoma	23	10.65

NET: Neuroendocrine tumor, SD: Standard Deviation

Nineteen patients were operated on after the diagnosis, and 5 patients with a locally advanced tumor located in the rectum were operated on after neoadjuvant therapy. One patient whose rectum biopsy showed malignancy received adjuvant chemotherapy since he also had lung and bone metastases at the time of diagnosis. Of the 11 patients with rectal tumors, 6 underwent low anterior resection, 4 underwent laparoscopic low anterior resection and 1 underwent abdominoperineal resection surgery. Five of the 8 patients who underwent anterior resection due to sigmoid colon tumor were operated on laparoscopically. Two patients with left colon tumors underwent laparoscopic

surgical resection and 3 patients with right colon tumors underwent open surgical resection.

In Table 3, the presence of dysplasia and malignancy was compared in terms of demographic, pathological, and colonoscopy data. Age (P=0.617) and gender (P=0.967) did not significantly affect the occurrence of dysplasia and/or malignancy among our patients. Dysplasia and/or malignancy were more likely to occur in the rectosigmoid region compared to the left and right colons (P=0.016). Among adenoma types, the risk of dysplasia and/or malignancy of villous polyps was higher compared to tubulovillous and tubular polyps, and those of tubulovillous polyps were higher than tubular polyps (P<0.01). The presence of dysplasia and/or malignancy were evaluated mutually between subgroups according to polyp size. There was no statistically significant difference in the incidence of dysplasia between the patient group with polyps sized 6-10 mm and 11-20 mm (P=0.192). Among all other subgroups, an increase in polyp size was found to cause a significant increase in dysplasia and/or malignancy (P<0.001).

Table 3: Comparison of the presence of dysplasia and malignancy with demographic, colonoscopic and pathological data

		No dysplasia n=83	Dysplasia n=105	Malignancy n=28	*P*-value
Age, median (Q1-Q3)		60 (55-64)	60 (55-65)	61.5 (56-65)	0.617*
Sex	Male	52 (39.1)	64 (48.1)	17 (12.8)	0.967
	Female	31 (37.3)	41 (49.4)	11 (13.3)	
Localization, n (%)	Rectosigmoid	57 (37.7)	72 (47.7)	22 (14.6)	0.016
	Left Colon	8 (22.2)	24 (66.7)	4 (11.1)	
	Right Colon	18 (62.1)	9 (31.0)	2 (6.9)	
Adenoma Type, n (%)	Tubular	57 (46.3)	65 (52.8)	1 (0.8)	<0.001
	Tubulovillous	5 (10.6)	37 (78.7)	5 (10.6)	
	Villous	0 (0)	3 (12.0)	22 (88.0)	
Polyp size, n (%)	≤5 mm	46 (59.7)	29 (37.7)	2 (2.6)	<0.001
	6-10 mm	27 (35.5)	45 (59.2)**	4 (5.3)	
	11-20 mm	10 (25.0)	22 (55.0)**	8 (20.0)	
	>20 mm	0 (0)	9 (39.1)	14 (60.9)	
Size, median (Q1-Q3) (mm)		4 (4-8)	8 (5-13)	23.5 (17-30)	<0.001*

* Mann-Whitney U test, mm: millimeter, ** In post hoc analysis, 6-10 mm and 11-20 mm polyps did not differ in terms of dysplasia.

Discussion

Early diagnosis of colorectal cancer in asymptomatic patients is facilitated by screening programs. Fecal tests and colonoscopy are widely used throughout the world. Colonoscopy is one of the most important analyses because it allows early diagnosis of these patients, obtaining pathological samples, and total removal of detected adenomas. But the fact that it is an invasive and uncomfortable procedure, and the large number of individuals to be screened are significant problems. For this reason, it is cost-effective to determine the patients to undergo colonoscopy by noninvasive diagnostic methods. Despite nuances, screening programs based on fecal immunochemical testing are mainly used around the world [5, 6]. A study comparing fecal tests and colonoscopy in screening showed that patients' participation in fecal tests was higher. Although the cancer detection rates of both screening methods are similar, colonoscopy was more successful in polyp detection rates [7].

In our country, fecal immunochemical testing is performed in the patient group aged between 50-70 years, and patients with fecal occult blood are referred for colonoscopy. In recent years, many suggested that the age for screening onset be set at 45 years [8], especially in areas with a high incidence of CRC and individuals with above-average risk. However, this will lead to an increase in the number of patients to be screened, bringing an additional burden [9]. The age at which screening will be stopped is controversial. Comorbid diseases, which increase with age, reduce the prolongation of life expectancy with screening. Female patients aged 90 years and males aged 85 years do not benefit from screening. The ages on which most are focused are 70 and 75 years. A person's health, life expectancy, and functional condition play a role in the age at which screening will be done [10].

The quality of colonoscopy to be performed in patients with positive fecal occult blood during screening is important. Colon cleansing is the most important reason affecting quality. A successful colon cleansing will increase the rate of reaching the cecum, as well as help increase the visibility of small polyps. Colonoscopy should be performed by experienced endoscopists, and the success of reaching the cecum should be above 95%. The process should not take less than 6 minutes, especially the return after cecum visualization [11]. In our center, the cecum could not be reached at the first try in a small number of patients because of a dirty colon. After the colon cleansing was repeated, the cecum was reached in all.

A polyp detection rate of >25% during colonoscopy for screening indicates good colonoscopy quality [12]. Corley et al. [13] reported polyp detection rates as 7.4%-52.5% for different endoscopists, and each 1% increase in polyp detection rate was associated with a 3% decrease in cancer risk. In our study, at least one polyp was identified in 216 (28.5%) patients colonoscopically. Studies report that the detection rate of colorectal cancer in screening patients ranges between 0.26%-4.1% [14-16]. In another large study in which 7503 consecutive cases not covered by the CRC screening program were discussed, the malignancy rate was reported as 4.1% in the histopathological examination of 611 patients with polyps [17]. In this study, patients with malignancy accounted for 3.69% of all patients and 12.96% of patients with polyps, which indicates that CRC screening patients with detected polyps are more likely to have a malignancy. Additionally, all our patients had early-stage tumors, except for one patient with metastasis at the time of diagnosis and 5 patients with progressive local tumor at the rectum.

Limitations

The main limitations of this study include its retrospective and single-center design. Second, there was no control group to increase the power of the current analysis. We think that the effectiveness of screening programs will be better demonstrated with multicenter, prospective studies.

Conclusion

The results of this study showed that colonoscopy performed on colorectal cancer screening patients with a positive FOB test was quite successful in diagnosing precancerous lesions and colorectal cancer. In addition, colonoscopy can prevent colorectal cancer by complete removal of detected lesions, and it is useful in the differential diagnosis of diverticular disease, colitis, and solitary rectal ulcer that may cause fecal occult blood positivity.

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Research article

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Plexin C1: A novel screening test for lung cancer

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Ethics Committee Approval
Ethics committee approval was received from the Non-invasive Clinical Research Ethics Committee of Van Yuzuncu Yil University, Van, Turkey (Decision No: 2020/03-17, Date: 22.05.2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Lung cancer, where early diagnosis is particularly important, is one of the leading causes of death worldwide. Unfortunately, patients with lung cancer present at advanced stages. Biomarkers are needed to detect cancer at an earlier stage. In the present study, we aimed to emphasize that Plexin C1 level can be used in the early diagnosis of patients with lung cancer.

Methods: This prospective case-control study included 50 patients with lung cancer who presented between May 2020-September 2020 (25 males and 25 females) in the patient group and 40 healthy individuals (23 males and 17 females) in the control group. All patients with lung cancer underwent routine preoperative tests. Additionally, the preoperative Plexin C1 levels of all patients were measured with the ELISA method and compared between the patient and control groups, and with respect to cancer staging.

Results: The median Plexin C1 levels in the patient and control groups were 9.5 ng/mL and 4.0 ng/mL, respectively (P<0.001). The patients with Stage 4 tumors had significantly higher serum Plexin C1 levels than those with Stage 1, Stage 2, and Stage 3 tumors (P<0.001). Also, Plexin C1 levels were higher in patients with greater depth of invasion (P<0.001), more lymph node involvement (P<0.001), and distant metastasis (P<0.001).

Conclusion: Plexin C1 can be used as a predictive biomarker at the time of diagnosis for lung cancer, and for cancer stage discrimination to show early, advanced, or metastatic disease.

Keywords: Lung cancer, Plexin C1, Biomarker, Tumoral stage

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide [1]. In contrast to other cancers, the 5-year survival rate in lung cancer, as well as pancreatic and gastric cancers, only mildly increased in recent years [2]. A lower rate of diagnosis at earlier stages is a significant factor affecting the low survival rate. Although the challenges associated with the early diagnosis of lung cancer underline the significance of imaging technologies, the economic burden of such advanced radio-diagnostic methods, radiation exposure, and false-positivity rates cause significant obstacles in their use.

Biochemical markers, which are becoming a popular and promising alternative in cancer diagnostics, stand out since they help in understanding the body's condition better than genetic biomarkers such as DNA. The discovery of these biomarkers and the clinical need were extensively examined and are considered by many to be clinically useful [3].

In previous studies, several biomarkers were identified for lung cancer, including carcinoembryonic antigen (CEA), cytokeratin-19 fragments (CYFRA 21-1), cancer antigen-125 (CA-125), and neuron-specific enolase (NSE) [4-8]. However, the development of a new biomarker for cancer diagnosis, experimental processes, and clinical applications require a considerable amount of effort and time. The approval of a biomarker as an indicator of diagnosis or survival in an organ cancer depends on its confirmation by several studies. Although proposed biomarkers often fail to meet the target criteria, innovative clinical applications continue to aim for the early diagnosis of malignancies [9].

The studies to develop novel lung cancer biomarkers suffer from similar problems as in the studies for other cancers. Protein biomarkers found in serum tend to show cross-reactivity with other cancers. Large-scale studies are needed before the ultimate confirmation of a molecule as a biomarker in clinical settings [10]. Moreover, immunoassay-based diagnostic methods are heavily dependent on the availability of monoclonal antibodies to detect these biomarkers. Thus, a few of several molecules identified as potential biomarkers eventually advance to be of clinical use.

This study aimed to show that the serum levels of Plexin C1 can be used for lung cancer stage discrimination.

Materials and methods

This prospective case-control study included 50 lung cancer patients enrolled between May 2020 and September 2020 (25 males and 25 females, 30 with adenocarcinoma and 20 with squamous cell carcinoma), and the control group included 40 healthy individuals (23 males and 17 females). After the surgery, the TNM classification for malignant tumors was used for pathological staging of cancer as described by the Union for International Cancer Control (eighth edition) [11].

The ELISA for Plexin C1 was performed with commercial kits (MyBiosource, Catalog No: MBS944227) according to the manufacturer protocol by using plates that were pre-coated with the primary antibody. Serum was transferred to wells, incubated with the antibodies, washed, and substrate solution was added, followed by the color-reagent and quenching solution. Finally, absorption at 450 nm wavelength was measured. The mean absorption value for duplicates was used for the analysis of each sample. The assay has high sensitivity and excellent specificity for human Plexin C1, with a typical limit of detection of 0.078 ng/mL and a detection range of 0.312-20 ng/mL. The assay was found to have no significant cross-reactivity with or interference from Plexin C1 analogs.

Statistical analysis

Normal distribution of the data was tested with the Shapiro-Wilk test, histograms, Q-Q plots, and box plot charts. The data were presented as median (25^{th} percentile-75^{th} percentile) and frequency (percentage). The Mann-Whitney U test was used for the comparisons of two groups. The Kruskal-Wallis one-way analysis of variance was used for the comparisons of three or more groups. The Dunn test was used for multiple comparisons. Nominal variables were evaluated with the Pearson chi-square test. The limit of significance was set as $P<0.05$ and bidirectional. The analyses were performed with NCSS 10 software (Kaysville, Utah, USA).

Ethics

Ethics committee approval was received from the Non-invasive Clinical Research Ethics Committee of Van Yuzuncu Yil University, Van, Turkey (Decision No: 2020/03-17, Date: 22.05.2020). All procedures in this study involving human participants were performed following the 1964 Helsinki Declaration and its later amendments.

Results

This study included 50 patients with lung cancer (25 males and 25 females) with a median age of 54.0 years (range: 50-60 years) as the patient group and 40 healthy individuals (23 males and 17 females) with a median age of 59.0 years (range: 49-69 years) as the control group. The most common T, N, and M stages were T_4 (64%), N N_2 (64%), and M_1 (82%). According to TNM staging, 7 patients were Stage 1, 7 patients were Stage 2, 11 patients were Stage 3, and 25 patients were Stage 4. Table 1 summarizes the clinicopathological characteristics of all patients.

Table 1: The clinicopathological parameters of the patients and controls

Parameters	Control group (n=40)	Patient group (n=50)
Age (year)	59.0 (55.0-61.0)	54.0 (53.0-55.0)
Gender (M/F)	23 /17	25/25
Data of patient group		
TNM stage (n, %)		
• Stage 1		7 (14.0%)
• Stage 2		7 (14.0%)
• Stage 3		11(22.0%)
• Stage 4		25(50.0%)
Depth of invasion (n, %)		
• T_1		5 (10.0%)
• T_2		5 (10.0%)
• T_3		8 (16.0%)
• T_4		32 (64.0%)
Lymph node metastasis (n, %)		
• N_0		9 (18.0%)
• N_1		9 (18.0%)
• N_2		32 (64.0%)
Metastasis (n, %)		
• M_0		9 (18.0%)
• M_1		41(82.0%)

The median Plexin C1 levels of the patient and control groups were 9.5 ng/mL, and 4.0 ng/mL, respectively ($P<0.001$). Serum Plexin C1 levels are presented in Table 2.

The patients with Stage 4 tumors had significantly higher serum Plexin C1 levels than those with Stage 1, Stage 2, and Stage 3 tumors ($P<0.001$). In addition, Plexin C1 levels

were higher in patients with greater depth of invasion (P<0.001), more lymph node involvement (P<0.001), and distant metastasis (P<0.001). Serum Plexin C1 levels of the patients stratified by their clinicopathological variables are presented in Table 3.

Table 2: Preoperative serum Plexin C1 levels of the patients and controls (Median (IQR: 25th percentile-75th percentile))

Parameters	Control group (n=40)	Patient group (n=50)	*P*-value
Age (mean, year)	59.0 (55.0-61.0)	54.0 (53.0-55.0)	<0.001
Gender (M/F)	23 (57.5%)/17 (42.5%)	25 (50.0%)/25 (50.0%)	0.479
Plexin C1 (ng/mL)	4.0 (3.0-4.0)	9.5 (6.5-12.5)	<0.001

Table 3: Preoperative serum Plexin C1 levels stratified by the patients' clinical and pathological variables (Median (IQR: 25th percentile-75th percentile)

Parameters	Plexin C1 (ng/mL)	*P*-value
TNM stage		<0.001
• Stage 1	5.5 (5.5-6.0)	
• Stage 2	7 (6.5-7.0)	
• Stage 3	8.5 (7.0-9.5)	
• Stage 4	12.5 (11.0-14.5)	
Depth of invasion		<0.001
• T_1	5.5 (5.3-5.8)	
• T_2	6.5 (5.8-7.3)	
• T_3	6.8 (6.5-7.0)	
• T_4	11.5 (9.6-13.8)	
Lymph node metastasis		<0.001
• N_0	5.5 (5.5-6.3)	
• N_1	7.0 (6.5-7.3)	
• N_2	11.5 (9.6-13.8)	
Distant metastasis		<0.001
• M_0	5.5 (5.5-6.3)	
• M_1	11.0 (7.8-12.8)	

Discussion

Lung cancer is a global health problem. In the light of the Cancer Statistics report of Siegel et al. [1], 235,760 new lung cancer cases are expected to be seen in the USA. The same report also predicted that approximately 131,880 people will die due to gastric cancer in the USA. Since the exact mechanism of lung cancer is not known, most patients present with advanced disease. Therefore, early diagnosis is important in the diagnostic process, and biomarkers are needed to solve the diagnostic problem. Plexin C1 proteins were studied in human studies before in different cancer types such as hepatocellular carcinoma, gastric carcinoma, and melanoma. However, no human studies report that Plexin C1 protein can be used as a prognostic biomarker in lung cancer. We aimed to solve this problem in the literature.

Plexin C1 is a type-1 transmembrane receptor within the extracellular segment that has homology to the Met family tyrosine kinase receptors [12-14]. Plexin C1 is commonly involved in actin cytoskeleton rearrangements and focal adhesions. Focal adhesions are dynamic structures that bridge cell-to-extracellular matrix adhesions in an integrin-dependent manner [15]. Plexin C1 signaling influences focal adhesion assembly/disassembly and induces cytoskeletal remodeling. Thereby, it influences the cellular shape, extracellular matrix adherence, and cell motility and migration [16-18].

It can be speculated that understanding Plexin C1 levels of a patient facilitates an approach to establish the aggressiveness or metastatic potential of cancer where its increase represents aggressive cancer or cancer with high metastatic potential. In lung cancer, progression in tumor invasion and depth are significant indicators of the severity of the disease. Increased level of Plexin C1 in the sample, compared to that in a control, is associated with a higher depth of invasion.

The cell-matrix adhesion is coupled to the cytoskeletal dynamics during cell migration. The activation of Plexin C1 may uncouple these processes, prevent the formation of adhesive complexes and lamellipodia, thereby hinder directional cell migration [19-20].

There are some studies about Plexin C1 level and cancer correlation in the English literature. According to the previous studies, Plexin C1 protein is upregulated in hepatocellular carcinoma cells [15, 21]. On the other hand, Ni et al. [22], showed that the Plexin C1 gene was highly upregulated in gastric cancer with a poor prognosis. The expression level of PLXNC1 could serve as an independent biomarker to predict a patient's overall survival according to the study of Chen et al. [23].

The molecular effect of Plexin C1 protein in cancer pathogenesis is still limited. In addition, there was no human study about plexin C1 serum levels among cancer patients. In this study, the Plexin C1 levels in patients with lung cancer were measured with the ELISA assay, and the levels in the patients with different stages of lung cancer were systematically analyzed. The study suggested that Plexin C1 expression was significantly higher in lung cancer compared to that in healthy controls, especially at advanced stages, which suggests its potential role in lung cancer pathophysiology.

Limitations

One of the limitations of this study is that the role and mechanism of action of expression of the Plexin C1 protein in lung cancer have not been confirmed; therefore, further analysis of the clinical features and mechanism of action as well as larger patient populations are required to confirm the results of the current study.

Conclusion

Delay in the diagnosis and treatment of lung cancer is an important problem. Plexin C1 may have an important role in lung cancer and elevated Plexin C1 expression may serve as a new biomarker.

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The role of right ventricular volume in the diagnosis of pulmonary embolism and morbidity prediction

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Ethics Committee Approval
Local Ethics Committee of Adnan Menderes University with the decision number of 2018/1292.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Pulmonary embolism is a quite common and usually fatal disease. This study aimed to investigate the predictive value of the right ventricular volume in terms of pulmonary embolism and its laterality using imaging techniques.
Methods: This case-control study included patients who underwent tomography with a pre-diagnosis of pulmonary embolism between January 2016 and January 2018. The study group included patients diagnosed with pulmonary embolism, while the control group consisted of those with an excluded diagnosis of embolism. The gender, age, echocardiography, right ventricular volume, embolism location, computed tomography results, morbidity, and mortality of the patients were recorded. Among 253 patients who underwent chest tomography with a diagnosis of pulmonary embolism, the data of 149 patients were obtained. There were 64 individuals in the control group and 85 individuals in the patient group.
Results: In the study group, the length of hospital stay was 10.0 (range, 15.0-6.0) days, the systolic blood pressure was 125.5 (28.8) mmHg, the diastolic blood pressure was 77.8 (17.8) mmHg, and the heart rate was 103.4 (28.1) min. The ROC analysis of right ventricular volume revealed 81.2% sensitivity and 67.2% specificity (AUC: 0.850; *P*=0.001; 95% CI 0.789-0.910; cut-off: 103.7) in showing pulmonary embolism. There was a positive correlation between right ventricular volume and D-dimer (r: +0.739, *P*=0.001) in the control group and no correlation between the two in the study group (r: -0.178, *P*=0.139).
Conclusion: Measuring the right ventricular volume with the software will contribute to the treatment and referral of patients with suspected pulmonary thromboembolism who underwent chest tomography. Thus, time and financial waste can be avoided by preventing unnecessary patient transfers, and early transfer of real patients can contribute to the reduction of mortality and morbidity.

Keywords: Right ventricular volume, Pulmonary embolism, Mortality

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Introduction

Pulmonary thromboembolism (PTE) is the 3rd leading cause of cardiovascular deaths [1] in the USA with an incidence of 0.5-1.0 per thousand people [2], although its prevalence varies between 3.9% and 16.6% in the analysis of autopsy data [3,4]. Therefore, despite the frequent occurrence of PTE, its diagnosis remains a major clinical challenge, because many diseases present with the same signs and symptoms.

The diagnosis of PTE [2] is based on the following: The D-dimer level, and radiological imaging findings. The imaging techniques currently used for diagnosis are chest x-ray, pulmonary angiography, CT, MRI, V/P scintigraphy [5], and dual-energy computed tomography (DECT). DECT is the most recent method [6].

Large CT companies have been developing volume-based software at high prices, and the major problem with this software is that the calculations have to be done on CT portals, not on personal computers (PCs) [7]. This causes personal and professional limitations for patient images.

Our study aimed to propose an affordable and practical way for measuring right ventricular volume with normal computer software to accelerate the diagnosis of pulmonary thromboembolism.

Materials and methods

This case-control study included patients who underwent tomography with a diagnosis of pulmonary embolism between January 1, 2016, and January 1, 2018. Ethics approval was obtained from the Local Ethics Committee of Adnan Menderes University with the decision number 2018/1292. At least 66 patients were required for medium effect size, alpha=0.05, two-way hypothesis, and 80% power. The study group included patients diagnosed with pulmonary embolism, while the control group consisted of those with an excluded diagnosis of embolism.

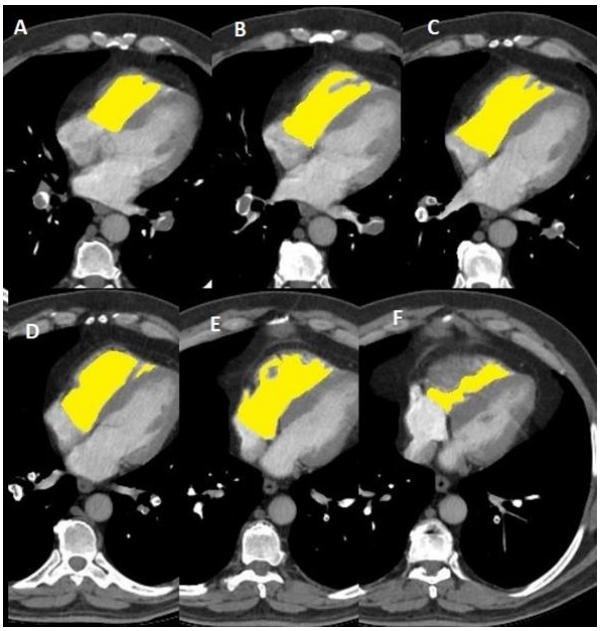
Patients over 18 years of age were included in this case-control study. Those who did not want to participate in the study, those with malignancies, those diagnosed with cor pulmonale and heart failure were excluded. All patients diagnosed with pulmonary embolism by CT were reviewed, the volumes of the right and left heart structures were calculated, and the results of transthoracic echocardiography performed after admission were noted.

Volume measurements were performed using the free-hand technique with Ekinoks advanced CT and MRI imaging Workstation software version 1.7.2017 (Telemed-Ekinoks software, Bogazici University Technopark, Istanbul, Turkey) (Figure 1). The pulmonary regions of interest were measured blinded to the diagnosis of the patients.

Statistical analysis

The data obtained from this case-control study were analyzed with SPSS 20 (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was performed to evaluate the distribution of the variables. When evaluating the differences between groups, the Kruskal-Wallis H test was used for the variables that did not conform to normal distribution. ROC curve analysis was performed to investigate the predictive value of right ventricular volume for pulmonary embolism. $P<0.05$ was considered statistically significant.

Figure 1: This image of a 1 mm-thick axial plane shows the sequential CT images (A, B, C, D, E, F) of a patient with pulmonary embolism in the craniocaudal direction. The sum of the area measurements from all sections gives the total right ventricular volume.



Results

Among 253 patients who underwent chest tomography with a diagnosis of pulmonary embolism between January 2016 and January 2018, the data of 149 patients were obtained. There were 64 individuals in the control group and 85 individuals in the patient group. The age, gender, right ventricular volume, and D-dimer distributions of the groups are shown in Table 1.

Table 1: Age, gender, right ventricular volume, and d-dimer distributions of the study groups

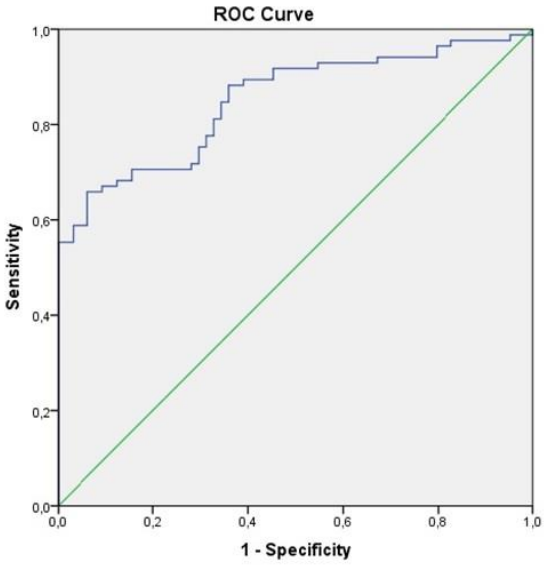
	Control n=64	Patient n=85	*P*-value
Age	69.3(12.5)	69.5(13.8)	0.968
Gender (Female)	15(44.1%)	35(42.2%)	0.755
Right ventricle volume	95.6(18.7)	150.3(51.0)	0.001
D-Dimer	359.3(103.0)	3293.6(1297.2)	0.001

The length of hospital stay (n=83), systolic blood pressure (BP) (n=37), diastolic BP (n=37) and heart rate (n=35) values of our study group were 10.0 (range, 15.0-6.0) days, 125.5(28.8) mmHg, 77.8(17.8) mmHg and 103.4(28.1) min, respectively. The volumes and the demographic data of our patient group are shown in Table 2. The ROC curve analysis between the control group and the patient group revealed a sensitivity of 81.2% and a specificity of 67.2% for right ventricular volume (AUC: 0.850; $P=0.001$; 95% CI 0.789-0.910; cut-off: 103.7) (Figure 2).

Table 2: Echocardiography findings of the patient group, deep venous thrombosis, embolism location, tissue plasminogen activator (tPA) treatment, volume analysis according to the type of embolism

		n(%)	Volume	*P*-value
Right Ventricular Dilatation in ECO	Positive	21(24.7%)	159.1(61.5)	0.285
	Negative	64(75.3%)	141.6(43.3)	
DVT	Positive	12(14.1%)	160.5(44.2)	0.191
	Negative	73(85.9%)	164.8(58.0)	
Side of embolism	Left	10(11.8%)	117.7(39.2)[a]	0.003[b&c]
	Right	30(35.4%)	133.7(42.7)[b]	0.005[a&c]
	Bilateral	45(52.8%)	168.6(51.8)[c]	
Treatment with tPA	Positive	14(16.5%)	166.8(52.3)	0.113
	Negative	71(83.5%)	142.9(48.5)	
Embolism	Massive	29(34.2%)	166.4(57.2)	0.036
	Submassive	56(65.8%)	142.0(45.9)	
Survival	Non-survivors	17(20%)	125.5(45.8)	0.020
	Survivors	68(80%)	157.4(50.4)	

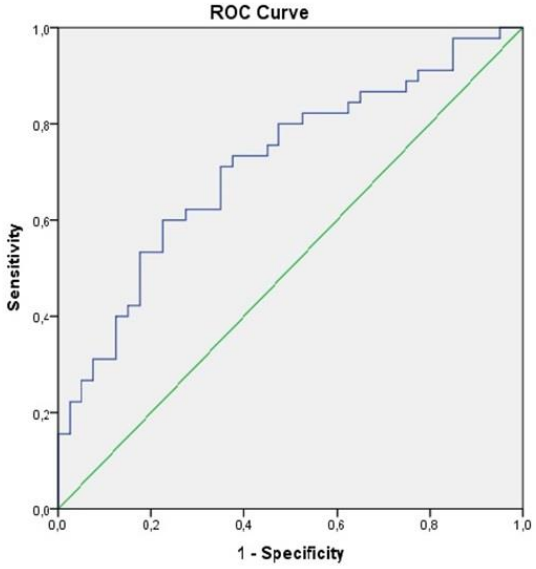
Figure 2: The ROC curve analysis of right ventricular volume (AUC: 0.850; *P*=0.001; 95% CI 0.789-0.910; cut-off: 103.7)



The correlation between volume and D-dimer was analyzed (Pearson's), which revealed r:+0.739 and *P*=0.001 in the control group and r:-0.178 and *P*=0.139 in the patient group.

The ROC curve analysis of right ventricular volume in terms of predicting whether the embolism was bilateral in the patient group revealed a sensitivity of 80% and a specificity of 52.5% (AUC: 0.716; *P*=0.001; 95% CI: 0.607-0.824; cut-off: 124.0) (Figure 3).

Figure 3: The ROC curve analysis of right ventricular volume in predicting whether the embolism was bilateral in the patient group (AUC: 0.716; p = 0.001; 95% CI: 0.607-0.824; cut-off: 124.0)



Right ventricular volume was insignificantly lower among patients with deep venous thrombosis compared to those without (44.2(12.8) vs. 58.0(15.0), p=0.834), while mean D-dimer values were significantly lower among those with deep venous thrombosis than those without (1004.3(302.8), 1186.1(342.4), *P*=0.027).

Discussion

Acute PTE affects at least one in a thousand people, and two-thirds cannot be diagnosed before death due to the nonspecific clinical presentation [8-10]. There are numerous risk factors for PTE, which include trauma obesity, pregnancy, surgery, immobilization, smoking, oral contraceptives, cancer, hormone replacement therapies, and a history of previous PTE or known coagulation disorders. The clinical presentation of PTE ranges from asymptomatic small pulmonary embolism with low mortality to a massive PTE resulting in right ventricular failure (RVF), shock, and/or death [11]. The hemodynamic response in PTE is not only dependent on the size of the embolism and the degree of pulmonary obstruction but also the physiological reaction of the vasoreactive substances released in response to this condition and the individual's cardiopulmonary infrastructure. In individuals without any cardiopulmonary disease, 25-30% of the vasculature must be occluded to increase pulmonary pressure. A normal RV can increase the mean pulmonary artery pressure to 40 mmHg with acute obstruction of 50-75% of the pulmonary vascular network by clot before RV failure occurs [12, 13].

Patients with right ventricular dysfunction have an increased risk of mortality and morbidity according to the guidelines. Pruszczyk et al. [14] found increased PE-related mortality when tricuspid annular plane systolic excursion measurement was ≤15, which indicates right ventricular dysfunction. The study by Ates et al. [15] also found higher mortality in the group with right ventricular dysfunction. A meta-analysis by Barco et al. supports this finding: RV dysfunction at admission was associated with early mortality [16]. In our study, RVF volume increase was significantly related to PE location and laterality.

The incidence of pulmonary embolism is increased among the elderly and causes a higher rate of mortality [17]. In their study, Arseven et al. [18] found no difference between the genders in terms of PE incidence. Sharif et al. [19] examined 1075 patients diagnosed with PE in the emergency department and found that the mean age of the patients was 48 years and 69.9% were female. In the study by Dogan et al. [20], 46.8% of 124 patients were female, with a mean age of 61 years. Although the male gender was more prominent in our study, the mean age was 69 years. There was no difference between the two groups in terms of gender and age.

In the study by Sista et al. [21], 90.8% of 87 patients had submassive or non-massive PE, while 9.2% had massive PE. Another study by Ates et al. [22] reported 218 massive, 235 submassive, and 186 non-massive PE in 639 patients diagnosed with PE. Similarly, of the patients in our study, 29 (34.1%) had massive and 56 (65.9%) had submassive PE.

The volume measurement technique comes to the fore, especially in peripheral hospitals, considering the low sensitivity of unenhanced tomography performed under normal conditions, the difficulty in contrast administration, the risk of nephropathy in contrast-enhanced tomography, and the fact that Dual Energy CT (DECT) cannot be performed everywhere. This technique provides the same sensitivity. An experimental study showed that the sensitivity of detecting PTE was 89% for DECT and 67% for conventional CT [23]. Another study reported per-patient sensitivity and specificity of 100% for detecting PTE (24). However, DECT offers a sensitivity of 60.0-82.9% and a specificity of 99.5-99.8% for detecting segmental and subsegmental PTE [24, 25]. Yet, the contact of the pulmonary segments with the upper mediastinum or heart chambers is considered a limiting factor for the appropriate evaluation of PTE by DECT [26]. In our study, the sensitivity for diagnosing

pulmonary thromboembolism with right ventricular volume measurement was 81.2%. Of course, the most sensitive diagnostic technique available should be used in central hospitals, but the measurement of the right ventricle in patients who are considered to have pulmonary thromboembolism will benefit the physician in distant hospitals.

Pulmonary embolism has a mortality rate of 25-30% in cases without early diagnosis and treatment [18]. Kempny et al. [27] examined 464,046 patients hospitalized with a diagnosis of pulmonary embolism in England between 1997 and 2015 in terms of mortality and found that the early mortality (1 month) was 15%. In our study, 17 (20%) patients died.

Limitation

To increase the power of the study, multi-centric studies with more patients are needed. Studies including distant hospitals, technological opportunities in terms of calculation, and patient transfer times will strengthen the results of our study.

Conclusion

The use of volume-measuring software that works in any computer instead of contrast-enhanced chest tomography will contribute to the treatment and referral of patients suspected of having pulmonary thromboembolism. Thus, time and financial waste can be avoided by preventing unnecessary patient transfers, and early transfer of real patients can contribute to the reduction of mortality and morbidity.

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Factors affecting the surgeon preference for bolus opioid use to control postoperative pain after bariatric surgery

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Abstract

Background/Aim: Pain control after bariatric surgery is important and inadequate control may lead to unwanted consequences. Although opioids remain an important therapeutic option in the management of postoperative pain, recent observations have pointed out to an increasing reluctance of surgeons to use opioid centered acute pain management strategies. This study aimed to examine the attitude and practice among bariatric surgeons regarding the postoperative use of opioids in acute pain management.

Methods: Sixty-seven surgeons actively involved in surgery for obesity and metabolic disorders who responded to a survey questioning their practical habits for postoperative pain management were included in this cross-sectional study. The questionnaire had a total of 16 multiple-choice questions on postoperative pain management. Potential factors affecting their preference for postoperative bolus opioid use were examined.

Results: Twenty-seven surgeons (40.3%) indicated that they prefer bolus opioid doses for postoperative analgesia. Surgeon age >55 years emerged as the only significant independent predictor for not preferring bolus postoperative opioid (OR: 0.19, 95% CI: 0.04-0.91, *P*=0.039). Main concern for opioid use was respiratory depression reported by 34.3% of the surgeons. Tramadol was the most preferred opioid (68.7%).

Conclusion: Relatively low number of bariatric surgeons seems to prefer bolus opioid administration after bariatric surgery to control acute postoperative pain. Older bariatric surgeons (>55 years of age) seem more reluctant. However, opioids, which should be used with caution in such patients with obesity, may be an option after bariatric surgery in selected patients.

Keywords: Bariatric surgery, Obesity, Opioids, Pain management, Postoperative analgesia

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Introduction

The global incidence of obesity is rising continuously, with approximately 650 million adults estimated to be affected as of year 2016 [1]. As a result of the increase in the number of individuals with obesity and morbid obesity, more patients have become candidates for bariatric surgery, leading to important questions regarding acute pain management during the perioperative period.

Despite advances in laparoscopic techniques, bariatric surgery is a time-consuming procedure, frequently causing moderate to severe postoperative pain [2]. Inadequate pain control may lead to sympathetic activation resulting in increased myocardial oxygen consumption and delay in the restoration of gastrointestinal motility [3]. Furthermore, it can reduce the oxygen supply to the myocardium [4]. Therefore, appropriate pain control bears significant clinical relevance in terms of the prevention of pain-related complications such as myocardial infarction, arrythmia, ileus, inadequate wound healing, and respiratory failure. It has been established that reduced postoperative pain is associated with a decrease in morbidity and mortality [5]. In this respect, it should also be noted that opioids remain an important therapeutic option in the management of postoperative pain [6].

However, recent observations have pointed out to an increasing reluctance of surgeons to use opioid-centered acute pain management strategies [7]. Among patients undergoing bariatric surgery, two reasons may help explain this tendency for not choosing opioids. First, patients with morbid obesity can experience opioid induced respiratory impairment associated with opioid-centric pain management strategies. This condition presents as sedation and respiratory depression attributed to opioid administration, combined with upper airway obstruction and hypercapnia. If undetected and/or untreated, it can cause significant mortality and morbidity, in addition to medico-legal problems [8]. Second, although ERAS protocols have become popular among surgeons and improved results are seen after this type of surgery, the published ERAS guidelines for bariatric surgery (ERABS) include recommendations disfavoring opioid use in weight loss surgery [7]. On the other hand, opioid analgesics remain at the top of The New Ottawa Ladder (the new "Ottawa" ladder describes the stabilization of acute pain management by addressing pro-nociception at any point of the stepwise approach) and are used as rescue analgesics for post-operative pain treatment [8].

In this Nationwide Survey, we aimed to examine the attitude and practice among bariatric surgeons regarding postoperative use of opioids in acute pain management as well as the factors that have an impact on these attitudes and practices.

Materials and methods

This cross-sectional study included general surgeons actively involved in surgery for obesity and metabolic disorders who responded to a survey questioning their practical habits for postoperative pain management. The study protocol was approved by Marmara University Medical Faculty, Ethics Committee for Clinical Studies (date, January 3, 2020; number, 09.2020.126) and the study was conducted in accordance with the Declaration of Helsinki.

Subjects

A total of 110 general surgeons were contacted via e-mail and WhatsApp messenger application and asked to complete a questionnaire on their postoperative pain control practices and preferences. All participants were members of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) and the Turkish Obesity Surgery Society (TOSS). By design, this study intended to include all or accessible surgeons in the country through the help of two bariatric surgery societies. According to sample size estimation, a total of 52 patients would be necessary to detect a large effect size while comparing variables in terms of opioid preference, with an alpha error = 0.05 and beta = 0.2 (power = 0.8). Since online response rate was not predictable, questionnaires were sent to all potential subjects. General surgeons were allowed for 45 days to complete the questionnaire. Several efforts were made to increase response rate and minimize bias related to on line methodology: (1) a reminder e-mail was sent every two weeks, (2) questions were multiple choice to simplify response, (3) e-mails were sent to personal e-mails rather than business e-mails, (4) in some cases non-responders were contacted with phone, and (5) administrators of the societies cooperated and helped with the acquisition of data. Sixty-seven general surgeons responded with completed questionnaire; thus, they were included in the analysis.

Questionnaire

The questionnaire had a total of 16 multiple-choice questions on demographics, job/academic title, institution, accreditations, and practices/preferences for postoperative pain management (drugs including opioids, dosing, patient-controlled analgesia, local methods, and preferences for postoperative nausea vomiting). Outcome measure was the preference of postoperative bolus opioid use (excluding opioid use as a part of patient-controlled analgesia). Potential factors affecting the preference for postoperative bolus opioid use was examined.

Statistical analysis

IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL) was used for the analysis of data. Descriptive data were presented in number (percentage). Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Stepwise logistic regression (forward conditional) was done for multivariate analysis to identify the significant independent surgeon/institution related predictors of opioid preference. Two-sided *P*-value <0.05 indicated statistical significance.

Results

Subject characteristics

A total of 110 bariatric surgeons were contacted and 67 (60.9%) responded. Thus, 67 subjects who completed the questionnaire were included in the analysis. Most subjects were male (98.5%, M/F: 66/1).

Postoperative opioid preference

Among 67 subjects, 27 (40.3%) indicated that they prefer bolus opioid doses for postoperative analgesia; however, 40 (59.7%) did not prefer to use additional opioid doses during the postoperative period. Main concerns for postoperative opioid

use were as follows, in decreasing order of frequency: Respiratory depression (34.3%), mobilization problems (28.4%), nausea/vomiting (26.9%), sedation (23.9%), urinary retention (9.0%), and others (10.4%). A minority reported no reason for not preferring opioids (4.5%). Tramadol was the most preferred opioid (68.7%), followed by pethidine (37.3%), morphine (6.0%), and fentanyl (1.5%). Most common reference for opioid dosing was total body weight (40.3%).

Predictors of opioid preference

Table 1 shows the univariate analysis of the surgeon/institution related factors that may be associated with opioid preference, where surgeon age >55 years, accredited institution, and preference of patient-controlled analgesia were associated with less likelihood of opioid preference. Surgeon age >55 years emerged as the only significant independent predictor for not preferring bolus postoperative opioids (OR, 0.19; 95%CI, 0.04-0.91, *P*=0.039).

Table 1: Univariate analysis of the surgeon/institution related factors that may be associated with opioid preference

Characteristics	Opioids not preferred (n=40)	Opioids preferred (n=27)	*P*-value
Demographics of the surgeon			
Age >55 years	12 (30.0%)	2 (7.4%)	0.033
Male sex	39 (97.5%)	27 (100.0%)	1.000
Academic title [a]	18 (45.0%)	14 (51.9%)	0.582
Characteristics of the healthcare facility			
Training hospital	20 (50.0%)	13 (48.1%)	0.882
Accreditation present [b]	15 (37.5%)	4 (14.8%)	0.043
Surgeon's practical approach			
Surgeon determines POA	35 (87.5%)	26 (96.3%)	0.389
Uses PCA	16 (40.0%)	4 (14.8%)	0.027
Uses local methods [c]	33 (82.5%)	20 (74.1%)	0.405
Opioid dosing approach [d]			
Accrued dose	20 (50.0%)	19 (70.4%)	0.097
Low dose	20 (50.0%)	8 (29.6%)	
Uses PONV medication [e]	28 (70.0%)	19 (70.4%)	0.974

POA: postoperative analgesia, PONV: postoperative nausea vomiting. [a] Professor or Associate Professor. [b] Any accreditation from a national or an international bariatric surgery society. [c] Thoracal injection, 94.3%; ultrasound-guided transabdominal plain block, 13.2%; transabdominal plain block, 7.5%; others, 5.6%, some subjects reported to use more than one local method. [d] Personal dosing approach when using in case it is necessary, even not prefers opioids. [e] Ondansetron, 49.3%; metoclopramide, 16.4%; dexamethasone, 4.5%.

Preferences of local methods

Local methods were preferred by 53 surgeons (79.1%). For those who prefer local methods, infiltration to the trocar site was the most preferred method (94.3%), followed by ultrasound-guided transversus abdominis plane (UTAP) block (13.2%), transversus abdominis plane (TAP) block (7.5%), and others (5.6%).

Discussion

In this study, the primary determinant of opioid use and preference among bariatric and metabolic surgeons was the surgeons' ages. Although accreditation status of the center and preference for the use of patient-controlled analgesia devices were other significant factors in univariate analysis, their predictive value was lost in the multivariate analysis. To the best of our knowledge, no previous studies examined the postoperative analgesia management and opioid preferences among bariatric and metabolic surgeons.

Although a few previous studies investigated obesity surgery and the age of the surgeon, these were mainly concerning the choice of surgery and postoperative complications [9]. In one study by Satkunasivam et al. [10], higher surgeon age was associated with lower rate of postoperative complications and mortality, which was explained by the selection of patients with a lower risk of complications. One potential reason for the reduced use of opioids by more senior surgeons in our study may be related with the concerns regarding opioid-related complications. In contrast with our findings, Santosa et al. [11] found higher preference of opioids by more senior surgeons, while younger surgeons were more likely to opt for non-opioid analgesics. The authors explained their findings by the lack of adequate training and guideline knowledge as well as failure to develop good communication with patients postoperatively. Our literature search failed to identify any studies examining the factors that have an impact on the choice of postoperative analgesia management and opioid use among bariatric and metabolic surgeons. Reluctance of more senior surgeons over 55 years of age to use opioids may be related with their more cautious attitudes based on their clinical experience [10].

Of the surgeons reporting no preference for opioid use, 37.5% were employed in an accredited clinical unit, where surgeons usually have to adhere to many clinical protocols [12, 13]. It has been already established that accreditation is associated with reduced postoperative complications and improved patient care in bariatric surgery centers [12]. However, this parameter did not emerge as an independent predictor in our study, probably due to the small sample size. It should also be noted that we found no published evidence regarding the link between the accreditation status of a bariatric surgery unit and opioid use among patients.

Our study appears to suggest that majority of bariatric and metabolic surgeons in our country disfavor the use of opioid analgesics in their patients. Again, in many recent papers, a trend toward reduced use of opioids has been described and the concept of "opioid-free analgesia" has been put forward [14]. One of the most important reasons for the reluctance to use opioids among surgeons is these agents' tendency to be associated with respiratory problems [14]. Similarly, in our study the most cited reason (34.3%) for not using opioids was their ability to cause respiratory depression.

On the other hand, tramadol was the most preferred opioid in this study. In patients undergoing obesity surgery, tramadol is reported to be safer and associated with reduced incidence of side effects as compared to other opioids, while providing adequate analgesia [3, 4]. Apart from opioid analgesics, NSAIDS were also frequently preferred by the surgeons, despite many recent studies reporting adverse consequences such as ulceration at anastomotic line and increased risk of bleeding [4, 15].

When asked about the weight criteria used for dose calculations regarding opioids, 40% of the participating surgeons in this study responded by stating that they used the "total bodyweight" for this purpose. On the other hand, as suggested by many recent findings, ideal bodyweight may be a more appropriate parameter for dose considerations, since the former approach may be related with several complications, mainly respiratory depression [4, 16].

Different local and regional pain management strategies are now being used by surgeons and anesthesiologists to reduce opioid use, including local anesthesia administration at the trocar incision site, TAP block, epidural block, and other types of truncal blocks [17]. In our study, the most preferred local method involved the use of local anesthesia at trocar incision site in line

with the published literature. The reasons for its frequent use include the low cost and practicality, as well as the fact that it does not require ultrasound or any other special equipment and knowledge [17]. Other types of truncal or epidural blocks may pose specific challenges in patients with morbid obesity, including the requirement to pinpoint anatomical landmarks using both manual and ultrasonographic techniques. Several authors reported almost equal efficacy of ultrasound-guided TAP block, a recently popularized approach, to local anesthesia at the trocar incision [18].

Although our results indicate a trend toward reduced use of opioid agents in patients with obesity, these drugs maintain their position as a significant and final step in pain management. In order to reduce the likelihood of complications, their doses should be administered based on ideal or lean bodyweight under close monitoring.

One of the limitations of our study is the lack of questions posed to the surgeons regarding the use of ERAS protocol in their procedures. In centers adopting the ERAS protocol, opioid use is reduced in favor of more frequent use of multimodal analgesia protocols. Another limitation relates to the relatively small sample size. In addition, the use of online questionnaire may be considered a limitation and a source of bias. However, as mentioned in the Methods section, we made efforts to minimize such bias. On the other hand, the main strength of our study comes from its ability to reach most actively working bariatric surgeons in the country with the cooperative help of the societies. Nevertheless, larger studies with better methodological design, probably with a face-to-face interview, would shed more light on the opioid preference of bariatric surgeons in the future.

Conclusion

Our findings suggest that a relatively low number of bariatric surgeons prefer bolus opioid administration after bariatric surgery to control postoperative pain and older surgeons seem to be more reluctant. Since inadequate postoperative pain control would lead to unwanted consequences in obese patients after bariatric surgery, opioids may be a viable option in selected patients where other methods do not provide adequate pain relief. However, caution should be exercised in patients with obesity for adequate dosing and potential complications, particularly respiratory depression.

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Learning process and results in endoscopic saphenous vein harvesting technique

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Previous Presentation
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Abstract

Background/Aim: Endoscopic saphenous vein graft harvesting (EVH) has been increasingly used in coronary bypass graft (CABG) surgery in recent years due to its cosmetic advantage and reduced morbidity. However, for the successful application of this technique, a learning process is required. In this study, we aimed to compare the results of the experience we obtained in the initial phase and later periods of the EVH technique.

Methods: Forty patients who underwent elective CABG between July 2015 and April 2017 were included in this retrospective cohort study. The first 20 patients (Group 1) and the next 20 patients (Group 2), whose saphenous vein graft (SVG) was prepared with the EVH technique were compared. The length and preparation time of SVGs prepared with EVH, local findings such as hematoma, necrosis, wound infection, and healing, demographic data, comorbidity, intraoperative and postoperative data, postoperative intensive care and hospitalization times, cosmetic satisfaction and wearing compression stockings were recorded.

Results: While the mean operation time was 201.4 (25.0) minutes in Group 1, it was 184.6 (17.1) minutes in Group 2 (P=0.018). There was no difference in the mean SVG lengths between the groups (P>0.05). While SVG preparation time was 75.3 (26.2) minutes in Group 1, it was 35.4 (6.0) minutes in Group 2 (P<0.001). The number of minor branch injuries in the SVG in Groups 1 and 2 were eight (40%), and two (10%), respectively, and all underwent primary repair (P<0.001). Mean length of hospital stay was similar between the groups (P=0.955). No hematoma, infection or necrosis requiring surgical intervention was observed in the extremity from which the SVG was taken. The use of compression stockings was longer in group 1 than in group 2 for the reduction or complete disappearance of edema (56.4 (23.3) vs 42.0 (19.4) days, P=0.040). No patient in any of the groups required rehospitalization due to infection at the saphenous vein incision site and incision healing problem. According to the satisfaction survey, cosmetic satisfaction was high in both groups (P=0.530).

Conclusion: We think that after the completion of the learning process on twenty patients, the EVH technique can be used more widely, with much better results in terms of both patient cosmetic satisfaction and reducing morbidity.

Keywords: Coronary artery bypass, Vena saphena magna, Endoscopic graft harvesting, Learning process

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Introduction

Coronary artery bypass surgery (CABG) is widely used in coronary artery disease (CAD) [1]. Autogenous grafts are generally used for bypass during surgery, mostly including the vena saphenous magna (VSM), internal mammary artery (IMA) and radial arteries [2].

Since it is a vein, VSM has a lower long-term patency rate than other arterial grafts, primarily because of intimal hyperplasia and thrombus [3]. Despite this, the fact that VSM is easily accessible and easy to prepare still makes it an indispensable graft [4]. It is possible to obtain an average 60-70 cm long graft by extending to the inguinal region with an incision starting from the anterior side of the SVG medial malleolus [5]. Complications such as pain, edema, surgical site infection, bleeding, hematoma, fat necrosis, keloid, seroma, and opening in the incision can be seen in the incision sites after SVG preparation with the conventional surgical method [6].

Classically, the SVG is removed subfascially by making a skin incision along its anatomical trace, tying its branches, and separating it from the surrounding tissues. The SVG requires much manipulation during preparation, which causes intimal damage and reduces the long-term graft patency rate [7]. Therefore, it has led to the search for different methods for reducing complications and longer-term graft patency. Other methods are the no-touch method (removal of the vessel with peripheral supporting tissues), the in-situ method (no graft transection until anastomosis), and SVG preparation with intermittent skin incision [8]. However, it has been shown that each method has advantages and disadvantages in terms of complications and graft quality [9]. Recently, due to these incision site problems, endoscopic non-touch SVG preparation with a small incision has come to the fore as an alternative method [10]. In this method, VSM is followed through a small 2-3 cm incision made in the knee region with the help of endoscopy, its branches are cauterized, and SVG is prepared with less manipulation and complications [11]. EVH technique is performed using special systems. Complications such as graft injury and hematoma may develop during SVG preparation, especially if the personnel are inexperienced. Despite the advantages of EVH over other methods, it has not been widely used in practice [12].

In this study, we aimed to share our results obtained by evaluating the surgical morbidity in the initial and progressive stages of the learning process of the EVH technique and the findings in the grafted extremities.

Materials and methods

Forty patients who underwent elective CABG at Giresun Private Ada Hospital Cardiovascular Surgery Clinic between July 2015 and April 2017 were included in this retrospective cohort study. The study was approved by Karadeniz Technical University Scientific Research Ethics Committee (Date: 31.12.2018, No: 2018/247). The study was approved by the university/local human research ethics committee and all procedures were conducted in accordance with institutional and national research committee ethical standards, the 1964 Declaration of Helsinki and subsequent amendments. All patients included in the study signed the consent forms for the operation.

Based on a statistical power analysis, a total sample size of twenty participants (ten per group) was needed to achieve a statistical power of 0.8 and a large effect size for total SVG harvest time (i.e., within-between groups) at an alpha level of 0.05. The sample size computation was based on the study by Davis et al. [13]. The first (Group 1) and last 20 patients (Group 2) in which full length SVGs were prepared using carbon dioxide insufflation with the EVH technique (The VasoViewTM HemoPro II System, MAQUET Getinge Group, Getinge AB, Gothenburg, Sweden) were compared. All operations were carried out by the same team.

Patients who had previous cardiac surgery, off-pump surgery, reoperation, emergency surgery and short segment saphenous vein grafts were not included in the study. The EVH method was not used in patients with a known history of venous insufficiency (deep or superficial) and who had undergone surgery on the extremity where SVG was to be prepared. Patients in which the SVGs had to prepared with the classical surgical technique during EVH were excluded from the study.

Patients' age, gender, body mass index (BMI), EUROSKORE (European System for. Cardiac Operative Risk Evaluation), ejection fraction (EF), presence of diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral artery disease and chronic renal failure were recorded. SVG harvesting time and SVG length, operation time, cardiopulmonary bypass time, cross clamp time, number of bypass anastomoses, time on the mechanical ventilator, atrial fibrillations, ventricular arrhythmias, acute renal failure, cerebrovascular events, perioperative myocardial infarction, amount of blood drainage, intraoperative and postoperative findings such as the amount of hospitalization, intensive care unit length of stay, length of hospital stay, and mortality were recorded. Local findings such as hematoma, burn, necrosis, minor branch injury, incision infection, lymphangitis, seroma, keloid in the extremity from which the saphenous vein graft was prepared with EVH technique were noted.

Pain, hyperemia, temperature increase, swelling and purulent discharge at the incision site were considered surgical site infection. After the patients were discharged in the postoperative period, control examinations were performed on the 10^{th} day, 1^{st} month and 3^{rd} month.

The cosmetic satisfaction survey results of the EVH procedure at the follow-up after the patients were discharged (patients were questioned whether they had small incisions and leg wounds) were evaluated on a patient-rated scale, as follows: 1- Not at all satisfied, 2- Not satisfied, 3- Satisfied, 4- Very satisfied.

Surgical method

VSM tracings, flow, and structural characteristics of the patients for whom SVG was to be prepared were evaluated with Doppler ultrasonography in the radiology clinic one day before the operation or in the operation room on the day of the operation. The mapping was done by marking the traces of the saphenous veins.

The VSM was found with an oblique 2-3 cm incision below the knee following the VSM trace. After the subcutaneous

tunnel was prepared by moving distally and proximally, the port was placed, and the balloon was inflated. The dissector device placed inside the endoscope was inserted into the tunnel by passing through the port, and carbon dioxide (CO2) insufflation (with 10-12 mmHg pressure and 4-5 l/min volume flow) began. With the endoscopic dissector, the VSM was released from the subcutaneous tissues along the desired length and its lateral branches were determined. The trunk of the VSM was preserved with the C-arm, and all lateral branches were cauterized and cut. The VSM seen from the camera was captured with a clamp advanced through 0.5 cm incisions made from the most proximal and distal points. Intravenous heparin was administered according to the patient's weight before transecting the VSM with its proximal and distal parts tied. Injuries in the SVG were repaired with 7-0 propylene suture. With the help of endoscope and C-arm, the leg was removed from the knee level incision and the lateral branches were ligated with 4/0 silk sutures (Figure 1a). SVG was kept in a mixture of physiological saline and autologous blood prepared with 5,000 IU heparin until anastomosis began. The 2 cm incision in the knee area was sutured one by one with 3/0 vicryl subcutaneous continuous and 3/0 propylene skin sutures, then, the proximal incision, 1 cm in length, was sutured with 3/0 propylene. The leg was wrapped with an elastic bandage from the ankle to the groin. After the bands of the patients were removed after 48 hours, compression stockings were put on until the groin. The patients were followed up for at least three months to terminate the use of compression stockings due to reduction or complete resolution of edema.

Figure 1: a) Full length SVG with EVH technique, b) Incision healing in the first month postoperatively

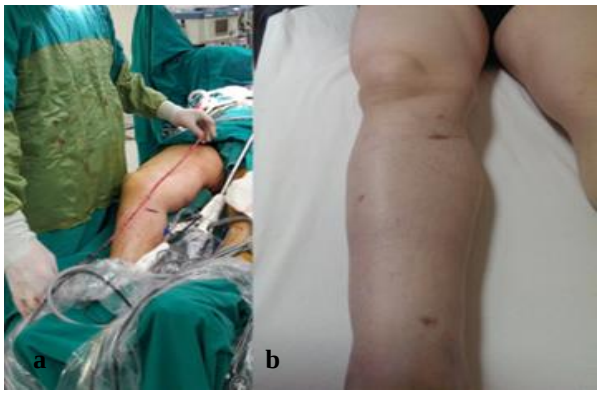
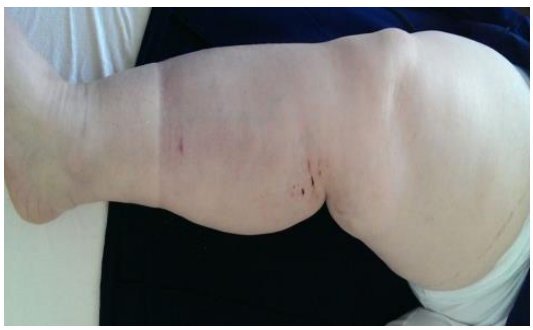


Figure 2: EVH application in an obese patient



Statistical analysis

Statistical analysis of the patients included in the study was performed with the SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) statistical program. Results were reported as mean (standard deviation (SD)) for numeric variables and as percentage (%) for categorical variables. Shapiro Wilk test was used to examine the distributions of the variables. Student's t-test was used to compare independent and numerical variables, while the Chi-square test was used to compare independent and categorical variables. A *P*-value of <0.05 was considered statistically significant.

Results

Of the 40 patients who participated in the study, 18 (45%) were female and 22 (55%) were male. The mean age of the patients was 66.5 (18.2) years in Group 1 and 65.1 (17.9) years in Group 2. There was no statistical difference between the preoperative characteristics of the patients (Table 1).

Table 1: Preoperative characteristics of patients

	Group 1 (n=20)	Group 2 (n=20)	*P*-value
Age (year), (mean (sd))	66.5 (18.2)	65.1 (17.9)	0.807
Gender (famale/male), n (%)	8 (40%) / 12 (60%)	10 (50%) / 10 (50%)	0.765
BMI (kg/m^2), (mean (sd))	27.3 (5.5)	28.2 (6.6)	0.917
EF (%), (mean (sd))	53.3 (7.7)	52.9 (8.6)	0.972
DM, n (%)	6 (30%)	8 (40%)	0.805
HT, n (%)	11 (55%)	12 (60%)	0.956
HL, n (%)	7 (45%)	11 (55%)	0.850
COPD, n (%)	3 (15%)	1 (5%)	0.742
CVD, n (%)	2 (10%)	1 (5%)	0.842
PAD, n (%)	7 (35%)	6 (30%)	0.768
CRF, n (%)	3 (15%)	2 (10%)	0.830
EuroSCORE, (mean (sd))	4.7 (0.9)	4.6 (1.1)	0.944

EF: Ejection fraction, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, PAD: Peripheral artery disease, CRF: Chronic renal failure, EUROSCORE: European System for Cardiac Operative Risk

SVG preparation time was 75.3 (26.2) minutes in Group 1 and 35.4 (6.0) minutes in Group 2 (*P*<0.001). Operation time was 201.4 (25.0) minutes in Group 1 and 184.6 (17.1) minutes in Group 2 (*P*=0.018). None of the patients died. Intraoperative and postoperative data are shown in Table 2.

Table 2: Intraoperative and postoperative data

	Group 1 (n=20)	Group 2 (n=20)	*P*-value
SVG harvesting time (minute), (mean (sd))	75.3 (26.2)	35.4 (6.0)	<0.001
SVG length (centimetre), (mean (sd))	51.3 (6.8)	54.1 (5.2)	0.745
Operation time (minute), (mean (sd))	201.4 (25.0)	184.6 (17.1)	0.018
CPB time (minute), (mean (sd))	85.6 (15.6)	89.1 (20.3)	0.892
CC time (minute), (mean (sd))	51.8 (9.7)	53.2 (10.5)	0.922
Number of bypass anastomosisn, n, (mean (sd))	3.9 (1.3)	4.2 (1.2)	0.866
Inotropic support, n (%)	8 (40%)	7 (35%)	0.790
Mechanical ventilator time (hour), (mean (sd))	9.8 (4.7)	9.5 (3.8)	0.960
Atrial fibrillation, n (%)	4 (20%)	7 (35%)	0.712
Ventricular arrhythmia, n (%)	1 (5%)	2 (10%)	0.842
Acute renal failure, n (%)	2 (10%)	1(5%)	0.842
Cerebrovascular event, n (%)	0 (0%)	1(5%)	0.954
Perioperative myocardial infarction, n (%)	0 (0%)	1(5%)	0.954
Blood transfusion (unit), (mean (sd))	3.5 (1.9)	3.3 (2.3)	0.946
Drainage amount (millilitre), (mean (sd))	720.0 (250.0)	710.0 (300.0)	0.979
Intensive care stay (day), (mean (sd))	2.1 (1.3)	2.2 (1.2)	0.955
Postoperative hospital stay (day), (mean (sd))	7.1 (2.6)	6.0 (2.4)	0.757

SVG: Saphenous vein graft, CPB: Cardiopulmonary bypass, CC: Cross clamp

During EVH, there were 8 minor VSM branch injuries in Group 1, and 2 minor VSM branch injuries in Group 2 (*P*<0.001). Compression stockings were used for 56.4 (23.3) days in Group 1, and 42.0 (19.4) days in Group 2 (*P*=0.40). No hematoma, necrosis, wound infection during hospitalization or that requiring hospitalization, wound dehiscence or lymphangitis were observed in either group. The findings in the SVG-harvested extremity are shown in Table 3.

Table 3: Postoperative findings of the saphenous vein graft harvested extremity

	Group 1 (n=20)	Group 2 (n=20)	*P*-value
Burned (n)	3	0	0.712
Minor branch injury (n)	8	2	<0.001
Seroma (n)	1	0	0.954
Keloid (n)	1	0	0.954
Compression stocking time (day), (mean (sd))	56.4 (23.3)	42.0 (19.4)	0.040
Patient cosmetic satisfaction (point), (mean (sd))	3.7 (0.3)	3.9 (0.1)	0.530

Discussion

The results of this retrospective study showed us that the EVH technique in CABG can be applied effectively as a result of a learning process. There are several factors that prevent or prolong the full recovery of patients after CABG surgery and thus reduce the benefit of CABG. CABG surgery is a major surgery in which large and deep incisions are made. This makes wound healing one of the most important problems that need to be tackled in the postoperative period [14]. Although SVG preparation in CABG is an important step of the surgery, it is traditionally prepared with long incisions or bridged incisions [15]. When performed with the conventional surgical method, the incision in each leg can be up to 85 cm long, making it one of the longest incisions of any routine surgery [16]. Various complications can be seen in the incision area after SVG preparation, especially in patients with risk factors such as obesity (BMI> 30), diabetes mellitus, peripheral vascular disease and female patient. Many complications such as edema, hematoma, non-healing incision site, keloid, fat necrosis, long incision scar, and surgical site infections may be encountered, especially after VSM removal [17]. As this situation may require re-hospitalization and revision in patients, it may keep the surgical team busy for a longer time, prolong the hospital stay and increase hospitalization costs. This impairs the patient's quality of life and reduces patient satisfaction [18].

Chernyavskiy et al. reported that wound complications, cosmetically unsatisfactory results may occur, and wound complications are seen in 2-24% of the cases, since large incisions are made in SVG preparation methods with the traditional surgical method [19]. There are studies showing that the incision sizes are shorter than the traditional method and the presence of intact tissues between the incisions reduces postoperative morbidity in the SVG harvesting technique with the bridged method [20]. However, it is known that this method has various technical difficulties and moreover, lateral branch injuries and vein dissections are frequently observed during traction of the saphenous vein. This, in turn, affects mid- and long-term graft patency [21]. In our study, wound complications in the extremity harvested with SVG were observed at a much lower rate in both groups when compared to the surgery methods.

Therefore, studies to develop an SVG preparation technique that is both less invasive and at least as safe as the traditional method, endoscopic interventions have begun to come to the fore, and the EVH technique in CABG surgery has begun to attract the attention of surgeons [22]. In this system, the subcutaneous tissue is inflated with carbon dioxide through a small incision made in the extremity and endoscopic SVG preparation is performed with the help of the tunnel formed [23]. This method is used in 80% of patients undergoing CABG surgery in the United States. Interestingly, the use of this technique in Europe has remained quite low, probably due to the high cost of endoscopic devices [24]. The reasons for this situation are unclear, but it has been stated that senior surgeons' resistance to change or reluctance to retrain may be associated with long operation time and additional cost [25].

The success of CABG depends on the long-term patency of the conduit used for revascularization [26]. However, it was concluded that this method may be associated with acute endothelial damage of the graft and endoscopic graft harvesting may promote a thrombogenic environment leading to a reduction in graft patency, which requires further investigation of the long-term patency of vascular grafts. This was seen as one of the factors preventing its widespread use by surgeons [27]. The effect of surgical graft harvesting with EVH on CABG outcomes in a meta-analysis study involving 26.525 patients, it was shown that no significant difference was found in terms of mortality, myocardial infarction, revascularization, angina recurrence, and vein graft stenosis during a mean follow-up period of 2.6 years [28]. In our study, there was no finding suggesting early graft failure such as ventricular rhythm disorder, myocardial infarction and mortality in both groups.

In a study, it was shown that the prolongation of the operation time causes the prolongation of the anesthesia period, and this may be associated with morbidity in the postoperative period [29]. According to the data obtained in our study, the mean operation time was significantly shortened in Group 2 as a result of the learning process. This operation time is similar to that of CABG operations, in which SVG is prepared by the classical surgical method [30].

In the study of Tamim et al. [31] using the EVH technique on 36 patients, the mean SVG harvesting time was 43.5 (9.5) minutes. This time decreased over time from 90 minutes to 25 minutes. The mean graft length obtained from the proximal limb was 45.0 (12.6) cm. In another study by Chiu et al. [32] on 1348 patients, they stated that the SVG harvesting time was 68 minutes on average in the first 50 cases and 23 minutes for the last 200 cases. The average SVG preparation time was 45 minutes in all cases. In our study, at the end of the learning process, the SVG preparation time was much shorter in Group 2 than in Group 1. It was halved in accordance with the literature and the process was completed before cannulation started. There was no difference in the mean lengths of the grafts prepared between the groups, and the necessary grafts were prepared for multiple bypass.

It has been reported in studies that the application of the EVH technique requires an important learning process. It is known that endoscopic vessel harvesting by inexperienced surgeons, more individual graft injuries and more tissue damage than EVH performed by experienced surgeons [33]. In our study, while there were 8 minor branch injuries in Group 1, 2 minor branch injuries were detected in Group 1. We think that the significant reduction in this injury is related to gaining the ability to maneuver more easily, to work faster and to solve potential problems by mastering the instruments used during EVH application with experience. In addition, it has been shown that gaining surgical skills to prepare endoscopic SVG and knowing in detail about the anatomy of the VSM facilitate the procedure [34]. In our study, we preferred to use preoperative and intraoperative ultrasonography for less manipulation of tissues and SVG.

EVH is known as a cost-effective method in CABG because it reduces wound complications and shortens hospital stay. The cost can be an important consideration when choosing an endoscopic approach for SVG harvesting. This method, along with the initial investment required for equipment, requires

additional costs for each operation due to the expense of disposable equipment. However, shortened hospital stays, savings due to improved wound healing and therefore less additional treatment can offset the additional cost of equipment [35, 36]. In our study, no difference was found between the postoperative hospital stay in Group 1 and Group 2. While there were skin burns in 3 patients, seroma in 1 patient and keloid in 1 patient in Group 1 in the SVG incision area, no hematoma, necrosis, hospital infection, wound healing problem, and infection requiring re-inpatient treatment were observed in both groups (Figure 1b).

It has been shown in many studies that the EVH technique is as safe as classical methods and significantly increases the cosmetic effect of the operated extremity [37]. It has been reported that EVH technique improves physical, social, emotional and mental health conditions and reduces physical role limitations [38]. Although there was no difference between the groups in our study, a high level of cosmetic satisfaction was found in both groups.

In the extremity for which SVG was harvested, edema may develop due to trauma, venous and lymphatic system circulatory disorders [39]. Morris et al. [40] revealed that there was more edema in the legs prepared with SVG with the classical surgical method. They stated that minimally invasive removal of the saphenous vein by endoscopic technique is more atraumatic for tissues. In our study, the duration of wearing compression stockings due to edema was found to be longer in Group 1. We think that this result is due to the fact that as the experience increases at the end of the learning process, the shortening of the procedure time is due to less trauma to the tissues.

Arıtürk et al. [41] in their study using the EVH technique on 100 patients, stated that after the completion of the SVG preparation learning process, technical and practical problems will be overcome, SVG preparation times will be shortened, and SVGs will be prepared in terms of quality as those prepared by the open method. In addition, the current literature suggests that surgeons with 100 or more EVH experience can prepare SVGs in shorter times with better graft quality and morbidity [42]. In this study, which we conducted on 40 patients, we think that this education process can be completed on fewer patients and that it can be applied with results compatible with the literature.

The first limitation of this study is that it is retrospective, the second limitation is that it is single-centered, and the third limitation is the inability to distinguish between risk factors for wound healing, such as diabetic, obes (BMI> 30), and female patients.

It is known that the EVH technique has very good results in patients with risk factors for the incision site [43]. Considering the costs, EVH may be preferred by surgeons, especially in patients with risk factors such as obesity, diabetes mellitus, peripheral artery disease and female patients (Figure 2). At the same time, we think that patients should be given a chance to choose by informing them about this alternative method.

Conclusion

As a result of this study, we think that after the completion of the learning process twenty patients, the EVH technique can be used more widely, with much better results in terms of both patient cosmetic satisfaction and reducing morbidity.

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An evaluation of regional anesthesia complications and patient satisfaction after cesarean section

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Ethics Committee Approval
Local Ethics Committee approval was obtained from Zekai Tahir Burak Women's Health Training and Research Hospital Ethics Committee on 26.12.2013 with the decision numbered 21. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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

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Abstract

Background/Aim: In obstetric anesthesia, regional techniques are considered advantageous for maternal mortality and morbidity. Nevertheless, serious or less severe complications related to regional anesthesia may occur. This study aimed to determine the postoperative early complications and assess postoperative pain and satisfaction of the patients by conducting a postoperative survey among those operated with regional anesthesia on the day after cesarean section.

Methods: All patients who underwent a cesarean section with regional anesthesia during the day within six months at our institution were considered for eligibility to participate in this cross-sectional study. On the day after the surgery, an anesthesiologist visited the patients and collected postoperative data, including demographic data and previous anesthesia experience, presence and intensity of the pain (current and from the operation until the postoperative visit), postoperative analgesia method, postoperative nausea, and vomiting (PONV), urinary catheterization, gas discharge, presence of backache, headache, shoulder pain, and initiation and the difficulties of breastfeeding. The patients were also questioned about their comfort during the operation, and their satisfaction with the anesthetic technique used.

Results: A total of 729 patients participated in the survey. Postoperative pain was managed with paracetamol and non-steroidal anti-inflammatory drugs in 696 (95.5%) patients, PCEA in 25 (3.4%) patients and intravenous PCA in 8 (1.1%) patients. Six hundred and ninety-three (87.7%) patients had pain at the time of the visit and the mean VAS score of current pain intensity was 4.2 (1.7). Seven hundred and twenty-two (99.0%) patients had pain between the end of the operation until the postoperative visit and the mean VAS score of maximum pain intensity was 6.4 (2.0). The mean time until postoperative pain began was 3.7 (2.4) hours. Among all, 48.7% of the patients experienced backache, 36.9% had shoulder pain, 17.8% had postoperative nausea, 6.6% had postoperative vomiting, and 20.2% had a postpartum headache. Breastfeeding was not initiated until the first postoperative day in 87.5% of the patients and the mean time until the onset of breastfeeding was 1.9 (2.8) hours. The intraoperative comfort and satisfaction with the anesthesia method were rated as good/very good by 74.7% and 84.4% of our patients, respectively.

Conclusion: Backache and shoulder pain are the most frequent minor complications in patients operated with regional anesthesia on the day after cesarean section. Determining and overcoming postoperative early complications is important for the satisfaction of patients after cesarean section.

Keywords: Cesarean, Regional anesthesia, Postoperative complications, Patient satisfaction

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Introduction

Obstetric patients differ from the other surgical populations because of concerns about the baby's exposure to anesthesia and peripartum surgical recovery needs, like breastfeeding and caring for a newborn baby. The choice of anesthesia type for cesarean section is affected by many factors. Anesthesiologists aim to prefer the safer and more comfortable method for the mother that is less harmful to the newborn.

In obstetric anesthesia, regional techniques are considered advantageous for maternal mortality and morbidity. Regional anesthesia has the advantage of an awake mother and minimal anesthetic exposure of the newborn baby. Regional techniques avoid the risks of general anesthesia like maternal aspiration, difficult airway, and failed intubation. It also enables the use of neuraxial opioids for post-operative pain.

The cesarean procedure is still associated with higher rates of maternal and perinatal mortality and morbidity. The overall postoperative morbidity rate associated with cesarean births is 35.7% [1]. The higher mortality and morbidity rates might be attributable not only to the surgical but also to the anesthetic procedures. Regional anesthesia techniques also have infrequent life-threatening complications. The most serious complications are from accidental intravenous administration of local anesthetics, administration of an overdose of local anesthetic intrathecally (total spinal) from unintentional subarachnoid placement, or migration of an epidural catheter. In addition to these serious complications, more frequent and less severe complications and side effects may occur with neuraxial blockade both intraoperatively and postoperatively, including inadequate analgesia, hypotension, nausea, shivering, urinary retention, motor weakness, elevated temperature, and a prolonged block. More serious postoperative complications like meningitis, epidural hematoma, and nerve or spinal cord injury are extremely rare [2].

This study aims to determine the postoperative early complications and assess the quantity of postoperative pain and satisfaction of patients by establishing a postoperative survey of patients operated with regional anesthesia on the day after cesarean section.

Materials and methods

After Local Ethics Committee approval (Zekai Tahir Burak Women's Health Training and Research Hospital Ethics Committee- 26.12.2013-21) was obtained, all patients who had a cesarean section with regional anesthesia during the day within six months were considered for eligibility. Exclusion criteria included being under 18 years of age, inability to communicate, having a history of chronic pain or opiate abuse, having a caesarian section after 4 p.m. (during the night shift), and admission to the surgical intensive care unit postoperatively. Informed written consent was taken from the patients before they were enrolled in the study.

In our institution, the routine practice of neuraxial anesthesia involves the prehydration of all patients intravenously with 1000 mL of lactated Ringer's solution. For spinal anesthesia and the spinal component of combined spino-epidural anesthesia (CSE), 10-13 mg hyperbaric bupivacaine and 10-20 µg of fentanyl are intrathecally administered via a 26-gauge needle inserted at the L3-L4 or L4-L5 interspace with an atraumatic spinal bevel. For epidural anesthesia, 15-20 ml of 0.5% bupivacaine is administered to the peridural area via an epidural catheter inserted at the L3-L4 or L4-L5 interspace. 50-100 µg of fentanyl is added to the local anesthetic solution. Metoclopramide 10 mg is routinely used for all patients for the prevention of nausea and vomiting.

Subsequent postoperative management is generally maintained by the surgical unit responsible for the patient. Patients are prescribed oral paracetamol (1g x 4) combined with intravenous tenoxicam 20 mg for routine postoperative analgesia. Patient-controlled epidural analgesia (PCEA) is not used routinely. When used, the PCEA device is programmed to give 5 ml of boluses of a solution of 0.5 $mg.ml^{-1}$ bupivacaine and 5 $\mu g.ml^{-1}$ fentanyl with a lockout interval of 20 min.

On the day after the surgery, an anesthetist visited the patients and collected postoperative data. The anesthesiologists who participated in interviewing the patients after their cesarean section were different from that who performed the intraoperative anesthesia. The questionnaire was administered via a face-to-face interview. The demographic data (maternal age, weight, height, education), previous anesthesia experience of the patients, type of previous anesthesia performed, presence and intensity of the pain (current and from the operation until the postoperative visit), postoperative analgesia method, time until decrement of motor block and first mobilization, the presence of postoperative nausea and vomiting (PONV), urinary retention, gas discharge, presence of backache, headache, and shoulder pain, and initiation and difficulties about breastfeeding. The patients were also questioned about whether they remembered the birth of their baby, their intraoperative comfort, satisfaction with the anesthetic technique used, if they would prefer the same method again in future surgeries, and their current pain level. Pain assessment was performed using a visual analog scale (VAS: 0–10 cm). The patients' intraoperative comfort and their satisfaction with the anesthetic technique used were assessed with a five-point scale as very good, good, average, bad, very bad.

Statistical analysis

Statistical analyses were performed using SPSS Software (Version 21.0, SPSS Inc., IL, USA). Categorical data were expressed as number and percentages (%) and continuous data, as mean (SD) (range).

Results

The total number of patients who had cesarean section within 6 months was 3210, 1128 of which had the operation during the day. General and regional anesthesia were administered to 276 and 852 patients, respectively. Among these 852 patients, 756 patients met the inclusion criteria, and 729 accepted to participate in the survey.

The demographic characteristics, previous anesthesia experience of the patients, and indications for cesarean section are detailed in Table 1. Postoperative analgesia was provided with paracetamol and non-steroidal anti-inflammatory drugs in 696 (95.5%) patients, PCEA in 25 (3.4%) and intravenous PCA in 8 (1.1%) patients. Six hundred and ninety-three (87.7%)

patients had pain at the time of the visit and the mean VAS score of current pain intensity was 4.2 (1.7). Seven hundred and twenty-two (99.0%) patients experienced pain between the operation until the postoperative visit and the mean VAS score of the maximum pain intensity was 6.4 (2.0). The mean time until pain onset after the operation was 3.7(2.4) hours. The mean times elapsed for decrement of motor block and the first mobilization were 3.9 (1.5) hours and 6.4 (1.9) hours, respectively (Table 2).

Table 1: Demographic characteristics, previous anesthesia experience of the patients and indications for cesarean section

Age (years), mean (SD)	29.0 (5.3)
Height (cm), mean (SD)	161(8.1)
Weight (kg), mean (SD)	77.8 (12.7)
Education level, n (%)	Unschooled 14 (1.9%)
	Primary school 200 (27.4%)
	Secondary school 175 (24%)
	High school 218 (29.9%)
	College 122 (16.7%)
Previous anesthesia, n (%)	No 226 (31%)
	Yes 503 (69%)
Previous anesthesia type, n (%)	General anesthesia 315 (43.2%)
	Regional anesthesia 155 (21.3%)
	General + regional anesthesia 33 (4.5%)
Indication of surgery,	History of previous cesarean 441 (60.5%)
n (%)	Cephalopelvic disproportion 90 (12.3%)
	Fetal distress 65 (8.9%)
	Breech presentation 57 (7.8%)
	Maternal disease 25 (3.4%)
	Twin pregnancy 21 (2.9%)
	Labor arrest 10 (1.4%)
	Oligo/polyhydramnios 7 (1.9%)
	Placenta previa 2 (0.3%)
	Pre-eclampsia 6 (0.8%)

Table 2: Pain and motor blockage characteristics of the patients

Current pain intensity (VAS), mean (SD)	4.2 (1.7)
Maximum pain intensity (VAS), mean (SD)	6.4 (2.0)
Start of pain (hours), mean (SD)	3.7 (2.4)
Decrement of motor blockage (hours), mean (SD)	3.9 (15)
First mobilization (hours), mean (SD)	6.4 (19)

The percentage of patients who had PONV, urinary retention, gas discharge, backache, headache, shoulder pain is presented in Table 3. The mean time elapsed until the first gas discharge was 12.3 (5.4) hours. A total of 638 (87.5%) patients began breastfeeding, within a mean time of 1.9 (2.8) hours. One hundred and fifty-five (21.3%) patients had difficulty with breastfeeding (Table 4).

Table 3: Presence of complications

	Yes, n(%)	No, n(%)
Nausea	130 (17.8%)	599 (82.2%)
Vomiting	48 (6.6%)	681 (934%)
Gas discharge	565 (77.5%)	164 (22.5%)
Urine retention	18 (2.5%)	711 (97.5%)
Headache	147 (20.2%)	582 (79.8%)
Backache	355 (48.7%)	374 (51.3%)
Shoulder pain	268 (36.9%)	460 (63.1%)

Table 4: Breastfeeding characteristics of the patients

Lactation, n(%)	Yes 638 (87.5%)
	No 91 (12.5%)
Start of breastfeeding (h), mean (SD)	1.9 (2.8)
Difficulty in breastfeeding, n(%)	No 463 (63.5%)
	Yes 155 (21.3%)
	Baby in neonatal unit 20 (2.7%)
	No lactation 91 (12.5%)

Patients' intraoperative comfort and their satisfaction with the anesthetic technique used are presented in Table 5. The percentage of patients who remembered the birth of their baby was 74.1%. Six hundred and ninety-six (92%) patients stated that the anesthesia method was chosen by the anesthesiologist, 56 (7.7%) patients said it was their own choice and 2 (0.3%) patients stated it as the surgeon's choice. Five hundred and seventy (78.2%) patients would prefer the same method again, 152 (20.9 %) would not and 7 (0.9%) patients were not sure.

Table 5: Intraoperative comfort and satisfaction with the anesthetic technique of the patients

	Comfort *n (%)	Satisfaction β, n(%)
Very good	213 (29.2%)	281 (38.7%)
Good	328 (45.0%)	333 (45.7%)
Average	144 (19.8%)	83 (11.4%)
Bad	34 (4.7%)	21 (2.9%)
Very bad	10 (1.3%)	11 (1.3%)

* Intraoperative comfort β satisfaction with the anesthetic technique

Discussion

Giving thorough information to the patients and personal care of the anesthesia team are the most important factors for patient satisfaction with anesthesia care [3]. A postoperative visit by the anesthesiologist can increase perceived 'continuity of personal care by the anesthesiologist' and satisfaction [4]. In addition to concerns about patient satisfaction, a postoperative visit is important to determine early complications and assess postoperative pain.

Several large studies are evaluating postoperative or intraoperative patient satisfaction or anesthesia complications. This prospective observational study focuses on postoperative early complications, pain, breastfeeding status, recovery characteristics of post-cesarean patients who received regional anesthesia.

The management of post-cesarean pain is particularly important as recovery is affected by pain. Satisfactory pain relief improves mobility and enhances breastfeeding and infant care in the postpartum period. According to the results of a study, pain is the most frequently identified postpartum problem among women who had a CS, and 79% reported experiencing pain after surgery [5]. In a descriptive study, Karlstro¨m et al. [6] reported that high levels of experienced pain during the first 24 hours after CS were common. A VAS score of 4 or greater was reported by 78% of patients and the median VAS rating was 6. We found that the mean VAS pain score on the first postoperative day was 4.2 (1.7), and the mean maximum pain intensity score was 6.4 (2.0). Postoperative analgesia was provided with paracetamol and non-steroidal anti-inflammatory drugs in 95.5% of patients. NSAIDs do not only provide postoperative analgesia but also relieve the discomfort of uterine cramps after vaginal delivery [7]. Hsu et al. reported that intraoperative administration of 20 mg tenoxicam produced a morphine-sparing effect for 33% and was sufficient to potentiate the analgesic effect of morphine on uterine cramping pain, but not on resting or evoked wound pain [8]. Our results are consistent with the previous studies. The combination of NSAIDs and paracetamol is synergistic for postoperative pain and is used by many units in the United Kingdom [9]. Paracetamol and NSAID combination is also compatible with Enhanced Recovery After Surgery (ERAS) regimens [10].

Surgical birth affects the onset and continuation of breastfeeding [11]. Women undergoing CS, particularly an emergency CS, are in the high-risk group for breastfeeding difficulties [12]. In our study, 87.5% of the patients had begun breastfeeding by the first postoperative day and the mean time for the onset of breastfeeding was 1.9 (2.8) hours. Kutlucan et al. [13] reported that the lactation onset was delayed in patients undergoing cesarean section with general anesthesia when compared with patients undergoing cesarean section with spinal and epidural anesthesia, and patients giving normal vaginal birth. The other three groups were similar in terms of lactation onset.

The mean time until lactation onset was 10.8(10.2) hours in their study. In another study, the mean time until breastfeeding initiation was 5.9 (1.9) hours in mothers who had a cesarean section with spinal anesthesia. Early contact between the mother and her newborn on the delivery table was the most important predictor of early breastfeeding [14]. Early establishment of breastfeeding within one hour after the cesarean section was higher in the postnatal support group than the usual care group (70.29% vs. 57.14%) in a study comparing the postnatal support for breastfeeding and usual hospital care [15]. The onset of breastfeeding in our study was earlier when compared with the results of Kutlucan et al. [13] and Awi et al. [14], possibly because our maternity hospital is accredited as a baby-friendly hospital and places emphasis on postnatal lactation support. Trained personnel help mothers make skin-to-skin contact immediately after delivery and initiate breastfeeding as quickly as possible.

Postdural puncture backache (PDPB) is one of the most common complaints after neuraxial anesthesia, with an incidence of 2% to 29% in adults [16, 17]. It is defined as the continuous pain that is localized around the site of spinal puncture which does not radiate [18]. The pathophysiology of PDPB includes muscular relaxation with stretching of spinal ligaments and/or localized tissue trauma [17]. In this study, we found out that 355 (48.7%) of patients experienced backache after a cesarean operation. Abdullayev et al. [19] reported the rate of backache as 62.4% with an Atracuan tip needle and 44.2% with a Quincke tip needle after cesarean operations. In another study, 29.3% of the patients experienced back pain on the first postoperative day [20]. The percentage of patients with backache in our study population is lower than that in Abdullayev and colleagues' study, despite the use of the same type of needle.

Shoulder pain is usually seen after laparoscopic surgery. However, recent studies suggest that shoulder pain is also seen after cesarean section [21, 22]. It is one of the consequences of cesarean section and is mostly underestimated. In this study, we found that 36.9% of patients had shoulder pain. Sharp pain observed in these patients was experienced in the shoulder area or under the diaphragm. The pain is described as originating from deep within the shoulder, or from the right chest, and usually disappears within 2-3 days after surgery. Zirak et al. [21] reported the prevalence of shoulder pain after CS as 39.45%, and the incidence of shoulder pain among cesarean patients by general anesthesia was higher than that of spinal anesthesia. This was attributed to air trapping, subdiaphragmatic clot, or peritoneal irritation. In another study, diaphragmatic irritation with amnion fluid or blood was the most important factor for shoulder pain after cesarean section. They reported the incidence of shoulder pain as 26.6 % among patients who had a cesarean section with spinal anesthesia [23]. Shoulder pain may be associated with breastfeeding difficulties. As seen in our study and the previous studies, the incidence of shoulder pain after cesarean section ranges between 26.6-39.6%, and more studies are needed focusing on the reason and the treatments of this complication.

The incidence of nausea and vomiting during regional anesthesia for cesarean delivery varies between 21%-79% [10]. They are reported to reduce patient satisfaction and delay hospital discharge. In our study, 130 (17.8%) patients experienced postoperative nausea and 48 (6.6%) had postoperative vomiting. We used 10 mg intravenous metoclopramide for routine nausea and vomiting prophylaxis in all our patients. Metoclopramide is a prokinetic agent which increases the tone of the lower esophageal sphincter. It also has an antidopaminergic action on the chemoreceptor trigger zone [24]. According to the results of a meta-analysis, metoclopramide is reported to cause a significant reduction in intraoperative and postoperative nausea and vomiting among patients undergoing cesarean section under neuraxial anesthesia without significant side effects [25].

Postpartum headache is the complaint of headache and neck or shoulder pain occurring within the first 6 weeks after delivery [26]. One prospective cohort study showed that 39% of women reported headaches in the first week after delivery, 75% were reported as primary headaches with the majority attributed to tension-type headaches, 4.7% were PDPH, and 8.1% were due to undetermined causes [27]. In another study by Stella et al., [28] tension and migraine headache were considered the cause in 47% of women, pre-eclampsia or eclampsia in 24%, and PDPH in 16% of the study group. In this study, we found out that 147 (20,2%) of our patients had a postpartum headache. Our results are consistent with the literature. Although most postpartum headaches are caused by temporary situations, more serious causes like cortical vein thrombosis, subarachnoid hemorrhage, posterior reversible leukoencephalopathy syndrome, subdural hematoma, cerebral infarction/ischemia, and meningitis must always be considered. All patients with headaches were further evaluated by our pain department.

Determining patient satisfaction enables evaluating the patient experience of anesthesia and may help to improve the quality of the anesthesia procedure. In our study, the number of patients who rated their intraoperative comfort as very good, good, bad, and very bad were 213 (29.2%), 328 (45.0%), 34 (4.7%), and 10 (1.3%), respectively. The number of patients who rated their satisfaction with the anesthetic technique as very good, good, bad, and very bad were 281 (38.7%), 333 (45.7%), 21 (2.9%), and 11 (1.3%), respectively. The bad and very bad ratings were evaluated as having had discomfort and dissatisfaction. The reasons affecting patient satisfaction or intraoperative comfort are not analyzed or discussed in our study. Many studies are focusing on this subject. In a study including all surgery types [29], the satisfaction rate was 96.8%, and moderate or severe postoperative pain, severe nausea and vomiting, and any other postoperative complications were related to patient dissatisfaction. In another study focusing on spinal anesthesia-related complications and reasons of satisfaction [30], postoperative pain at the surgical site, backache, and headache were major factors related to decreased patient satisfaction.

Conclusion

Backache and shoulder pain are the most frequent minor complications in patients operated with regional anesthesia on the day after cesarean section. Although routine pain control was established by obstetricians in the postoperative ward, a good follow-up of pain with a postoperative visit from the anesthesiology team might provide better pain control for patients. Determining and overcoming postoperative early

complications are important for the satisfaction of patients after cesarean section. Further studies which include more patients and longer-term follow-up may be needed.

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Should tumor size concern us in nonmetastatic colon adenocarcinoma?

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Ethics Committee Approval
This study was approved by the Kartal Dr. Lütfi Kirdar City Hospital ethics committee (approval date: 09.06.2021; approval number: 2021/514/203/3).
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Abstract

Background/Aim: Limited data are evaluating whether tumor diameter and the prognostic criteria are directly related to each other in colon adenocarcinoma cases. This study aimed to evaluate the relationship between tumor diameter and prognostic factors in non-metastatic colon adenocarcinomas.
Methods: Two hundred and sixty patients operated on due to colon adenocarcinoma and followed up in the General Surgery Department of our hospital between January 2015-December 2020 were included in this retrospective cohort study. The relationship between tumor size and lymphovascular invasion, perineural invasion, lymph node metastasis, and N-ratio was evaluated according to localization.
Results: The mean age of the patients was 63.3 (12.3) (min.-max.: 24-94) years. One hundred and sixty (61.5%) patients were male. The tumor was in the right colon (proximal to the splenic flexure) in 31%, and lymph node metastasis was detected in 43.5%. The number of metastatic lymph nodes and N-ratio values were similar according to tumor diameter (P>0.05 for each). Tumor diameter, the number of metastatic lymph nodes, and N-ratio values were not significantly correlated in the groups made according to localization (P>0.05 for each). The median tumor diameter was similar in patients with right colon and left colon cancer with and without lymph node metastasis. Likewise, no significant difference was found between the N stages in terms of median tumor diameter (P>0.05 for each).
Conclusion: Our findings show that tumor diameter is not directly related to lymph node metastasis or N-ratio in non-metastatic colon adenocarcinomas and that it does not provide reliable information about lymph node metastasis.

Keywords: Colon adenocarcinoma, Tumor diameter, Lymph node metastasis, N-ratio

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Introduction

Colon adenocarcinomas are one of the most fatal cancer types. In colon adenocarcinomas, a staging system based on the tumor's invasion depth in the tissue (T), lymph node involvement (N), and metastasis (M) status is used to determine the prognosis [1-3]. In recent years, studies investigated whether some findings such as the number of lymph nodes affected, N-ratio expressed as the ratio of this number to the number of lymph nodes removed during the operation, and tumor diameter provide information in predicting prognosis [1-4].

Various research states that the tumor diameter helps in predicting the prognosis in colon adenocarcinomas. It has been suggested that the tumor being large or small indicates a negative prognosis in some stages or some groups of patients, or that its evaluation together with lymph node involvement provides significant data [5-7]. All these reports show uncertainty about the relationship of tumor diameter to prognosis.

Limited data are evaluating whether tumor diameter and the prognostic criteria are directly related in colon adenocarcinoma cases. This study aimed to investigate the relationship between tumor diameter, perineural and lymphovascular invasion, lymph node metastasis, and N-ratio in colon adenocarcinomas.

Materials and methods

This retrospective cohort study was approved by the Kartal Dr. Lütfi Kirdar City Hospital ethics committee on 09.06.2021 with the decision number 2021/514/203/3.

Patients and tests

A total of 260 patients who were operated on with the diagnosis of colon adenocarcinoma and followed up in the General Surgery clinics of our hospital between January 2015-December 2020 were included in this study. Pathology and radiology results of the patients were obtained from the hospital automation system and analyzed.

Patients with unconfirmed diagnoses of adenocarcinoma, metastatic disease (stage 4), and tumors outside the colon (such as stomach, small intestine, and rectum) were excluded from the study.

Statistical analysis

SPSS 25.0 (IBM SPSS, Chicago, USA) was used for statistical analyses. Chi-Square test and Fisher's Exact Test were used for comparisons between groups of categorical variables. The assumption of normality in distribution was assessed with the Kolmogorov-Smirnov Test for continuous variables. The Mann-Whitney U Test and the Kruskal Wallis test were used to analyze the differences between continuous variables and multiple groups, respectively. Spearman's correlation analysis was utilized to analyze the association between continuous variables. The capacity of the number of nuclei to predict the presence of disease in patients was analyzed using receiver operating characteristic (ROC) curve analysis. The results were evaluated within the 95% confidence interval, and $P<0.05$ values were considered significant.

N-ratio was calculated as [4]:

N-ratio= (number of metastatic lymph nodes) / (number of lymph nodes removed).

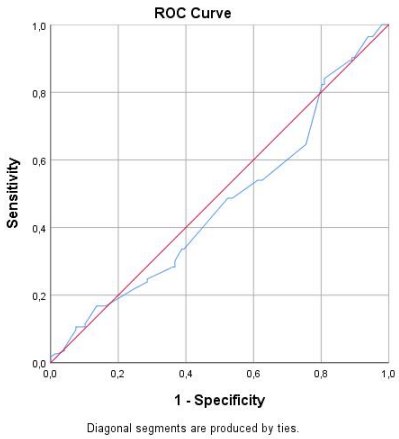
Power analysis was performed with G*Power Version 3.1.9.6 (Franz Faul, Universitaet Kiel, Germany), resulting in a need of 120 participants for 0.95 power with an effect size of 0.66.

Results

The mean age of the patients was 63.3 (12.3) (median: 63; interquartile range: 16; min.-max.: 24-94) years. One hundred and sixty patients (61.5%) were male. The tumor was in the right colon in 31% of the cases, and 14.6% were poorly differentiated. Perineural invasion was detected in 38.8%, lymphovascular invasion, in 45.8%, and lymph node metastasis, in 43.5% (Table 1).

ROC analyses revealed that a cut-off value of 44.5 mm for tumor diameter had a sensitivity of 54.0% and a specificity of 58.8% in predicting lymph node metastasis (AUC: 0.47; P=0.402; LB:0.399; UB: 0.541; CI 95%) (Figure 1).

Figure 1: ROC analysis. The cut-off value of 44.5 mm for tumor diameter had a sensitivity of 54.0% and a specificity of 58.8% in predicting lymph node metastasis (AUC: 0.47; P=0.402; LB:0.399; UB: 0.541; CI 95%).



In this study, the rate of patients with a tumor diameter above 44.5 mm was significantly higher among patients with a tumor in the right colon (P=0.004), while the rate of patients with a tumor diameter of less than 44.5 mm was significantly higher among stage 1 patients (P=0.031) (Table 1).

Table 1: Distribution of some variables by tumor diameter in all patients

	Tumor diameter (mm) <44.5 (n=109)		>44.5 (n=151)		Total	*P*-value
	n	%	n	%	n	
Gender						0.812
Male	68	42.5	92	57.5	160	
Female	41	41.0	59	59.0	100	
Localization						0.004
Right colon	24	28.9	59	71.1	83	
Left colon	85	48.0	92	52.0	177	
T						0.106
T1	4	80.0	1	20.0	5	
T2	13	56.5	10	43.5	23	
T3	67	41.4	95	58.6	162	
T4	25	35.7	45	64.3	70	
Differentiation						0.787
Well	14	37.8	23	62.2	37	
Moderately	80	43.2	105	56.8	185	
Poorly	15	39.5	23	60.5	38	
N						0.472
N0	57	38.8	90	61.2	147	
N1	29	47.5	32	52.5	61	
N2	23	44.2	29	55.8	52	
Stage						0.031
Stage 1	15	60.0	10	40.0	25	
Stage 2	42	34.4	80	65.6	122	
Stage 3	52	46.0	61	54.0	113	
Lymph node metastasis	52	46.0	61	54.0	113	0.241
Perineural invasion	45	44.6	56	55.4	101	0.493
Lymphovascular invasion	49	41.2	70	58.8	119	0.823

Chi square test was used.

The median tumor diameter of stage 1 patients with tumors in the left colon was significantly lower than those of stage 2 and 3 patients (P=0.005) (Table 2).

Metastatic lymph node count and N-ratio values were similar according to tumor diameter cut-off groups (P>0.05 for each) (Table 3).

Table 2: Comparison of median values

Stage		Age (years)	Tumor diameter (mm)
In all patients			
Stage 1	Mean	65.7	41.0
(n=27)	SD	12.7	22.1
	Median	65.0	40.0
Stage 2	Mean	63.4	54.3
(n=181)	SD	11.8	21.6
	Median	63.0	50.0
Stage 3	Mean	62.6	51.1
(n=52)	SD	12.6	23.6
	Median	63.0	45.0
P-value		0.478	0.016
Post-hoc			1<2; *P*=0.007
			1~3; *P*=0.072
			2~3; *P*=0.11
In the right colon-tumor patients			
Stage 1	Mean	72.8	68.0
(n=6)	SD	10.2	22.8
	Median	74.0	60.0
Stage 2	Mean	62.8	63.5
(n=53)	SD	13.3	21.9
	Median	62.0	60.0
Stage 3	Mean	62.2	56.1
(n=24)	SD	10.9	27.2
	Median	58.0	50.0
P-value		0.123	0.148
In the left colon-tumor patients			
Stage 1	Mean	64.0	34.2
(n=21)	SD	12.9	16.3
	Median	62.5	36.5
Stage 2	Mean	63.5	51.2
(n=128)	SD	11.4	20.7
	Median	64.0	47.0
Stage 3	Mean	62.8	47.6
(n=28)	SD	13.8	20.2
	Median	64.5	40.0
P-value		0.959	0.005
Post-hoc			1<2; *P*=0.001
			1<3; *P*=0.018
			2~3; *P*=0.202

Kruskal Wallis test was used for general comparison, and Mann-Whitney U test was used for comparisons between each pair. SD: Standard deviation.

Table 3: Comparison of median values according to tumor diameter groups

Tumor diameter		Age (years)	Number of metastatic lymph nodes	N-ratio
In all patients				
<44.5 mm	Mean	62.9	1.8	10.6
(n=109)	SD	11.5	3.0	18.4
	Median	64.0	0.0	0.0
>44.5 mm	Mean	63.5	2.1	11.1
(n=151)	SD	12.8	4.0	21.8
	Median	63.0	0.0	0.0
P-value		0.824	0.449	0.385
In patients with right colon tumor				
<44.5 mm	Mean	62.8	2.5	13.6
(n=24)	SD	11.2	2.7	20.3
	Median	60.5	1.5	5.8
>44.5 mm	Mean	63.2	3.0	15.1
(n=59)	SD	12.3	5.0	24.6
	Median	62.0	1.0	2.0
P-value		0.58	0.375	0.441
In patients with left colon tumor				
<44.5 mm	Mean	62.9	1.7	9.7
(n=85)	SD	11.7	3.1	17.8
	Median	65.0	0.0	0.0
>44.5 mm	Mean	63.7	1.5	8.5
(n=92)	SD	13.2	3.2	19.6
	Median	64.0	0.0	0.0
P-value		0.939	0.359	0.285

Mann-Whitney U test was used. N-ratio was calculated as: N-ratio=(number of metastatic lymph nodes) / (number of lymph nodes removed). SD: Standard deviation.

Tumor diameter, the number of metastatic lymph nodes, and N-ratio values were not significantly correlated according to localization (P>0.05 for each) (Table 4).

The median tumor diameter was similar among patients with right colon cancer and left colon cancer with and without lymph node metastasis. Likewise, no significant difference was found between the N stages in terms of median tumor diameter (P>0.05 for each).

Median tumor diameter was similar in patients with and without perineural invasion (P=0.741). The median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with perineural invasion than in those without (P>0.001 for both) (Table 5).

The median tumor diameter was similar between patients with and without lymphovascular invasion (P=0.58). The median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with lymphovascular invasion compared to those without (P>0.001 for both) (Table 5).

Table 4: Correlation analyzes

		Tumor diameter (mm)
In all patients		
Number of metastatic lymph nodes	r	0.071
	P-value	0.253
N-Ratio	r	0.050
	P-value	0.424
In the right colon-tumor patients		
Number of metastatic lymph nodes	r	-0.056
	P-value	0.613
N-Ratio	r	-0.098
	P-value	0.376
In the left colon-tumor patients		
Number of metastatic lymph nodes	r	0.107
	P-value	0.157
N-Ratio	r	0.104
	P-value	0.168

Pearson's correlation anaysis was used.

Table 5: Comparison of median values according to perineural and lymphovascular involvement

		Tumor diameter (mm)	Number of metastatic lymph nodes	N-Ratio
Perineural invasion				
Present	Mean	51.6	3.6	19.4
(n=101)	SD	24.8	4.7	25.0
	Median	50	2	10
Absent	Mean	51.7	0.9	5.5
(n=159)	SD	21.5	2.2	14.6
	Median	50	0	0
P-value		0.58	<0.001	<0.001
Lymphovascular invasion				
Present	Mean	52.6	3.6	18.9
(n=119)	SD	23.7	4.4	23.7
	Median	50	2	10.3
Absent	Mean	50.8	0.6	4.1
(n=141)	SD	22	2.0	14.1
	Median	48	0	0
P-value		0.741	<0.001	<0.001

Mann-Whitney U test was used. N-ratio was calculated as: N-ratio=(number of metastatic lymph nodes) / (number of lymph nodes removed). SD: Standard deviation.

Discussion

Colon adenocarcinoma, one of the most common cancers in the world, has a high mortality rate [8, 9]. The relationship between findings such as tumor diameter, lymph node metastasis, and N-ratio in colon adenocarcinomas has not been demonstrated [4-7]. We examined the relationship between these data and observed that lymph node metastasis was not related to the size of the tumor.

Tumor diameter can reportedly provide significant information in predicting distant metastasis and prognosis in colon adenocarcinomas [5, 10]. A study reported that the prognosis was worse in cases with large tumors in the presence of lymph node metastasis [11], while another study stated that smaller tumor diameter was associated with a worse prognosis in the presence of lymph node metastasis [12]. In some studies, smaller tumor diameter was associated with worse survival or more frequent recurrence in T4 [6], T4b [13], stage 2 [14], stage 2a [7, 15, 16], and stage 1-3 [17] cancers. Another study reported

that tumor diameter was associated with survival in stage 3 cases but did not provide significant information about prognosis in stage 2 cases [18]. These data show that the relationship of tumor size with prognosis has not yet been clarified. In our study, the rate of patients with a tumor diameter of less than 44.5 mm was significantly higher among those with stage 1 cancer, and the median tumor diameter was significantly lower among stage 1 patients with tumors in the left colon than in stage 2 and 3 patients. Tumor size may be associated with stage, especially in left colon tumors, and a smaller tumor size can be expected in the early stages in these cases.

There may be an increase in the number of involved lymph nodes as the tumor diameter increases in colon adenocarcinomas, which can be expected because larger tumors may cause a greater inflammatory response in the mesentery [19-22]. Some studies report that as the N stage increases, the median tumor diameter increases, and tumor diameter is associated with lymph node metastasis [23, 24]. However, another study revealed that the tumor diameter decreased as the N stage increased [17]. In a study, no relationship was found between tumor diameter and the number of metastatic lymph nodes [19]. Another study reported that the lymph nodes involved were larger due to the more intense immune reaction in cases with large tumor diameters [25]. These data do not prove a direct relationship between tumor diameter and lymph node metastasis. However, in one study, tumor diameter and the presence of lymph node metastases were significantly correlated [26]. In our study, the number of metastatic lymph nodes and N-ratio values did not differ with tumor diameter. In the groups made according to localization, there was no correlation between tumor diameter, the number of metastatic lymph nodes, and N-ratio values. The median tumor diameter was similar in both right colon cancer patients and left colon cancer patients with and without lymph node metastasis. Likewise, no significant difference was found between the N stages in terms of median tumor diameter. Our ROC analysis showed that the threshold value determined for tumor diameter in predicting lymph node metastasis had a very low level of reliability. All these findings show that there is no direct relationship between tumor diameter and lymph node metastasis.

Perineural invasion, the tumor invading the neurons around the organ, may indicate an unfavorable prognosis [13, 14, 16, 25]. In some studies, the tumor diameter did not differ according to the presence of perineural invasion [13, 16, 17]. In the present study, both the proportion of patients with large-size tumors and the median tumor diameter were similar in patients with and without perineural invasion, which indicates that perineural invasion is not directly related to tumor diameter.

Various studies state that the number of metastatic lymph nodes is significantly higher in patients with perineural invasion [17, 19, 25]. In ours, the median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with perineural invasion than in those without. This shows that perineural invasion and lymph node metastasis are directly related and more lymph nodes are involved in those with perineural invasion.

Lymphovascular invasion is the tumoral invasion of the lymphatic and vascular structures around the organ and may show an unfavorable prognosis [13, 14, 25]. Some studies showed that tumor diameter distribution does not differ according to the presence of lymphovascular invasion [13, 16, 17]. In our study, both the proportion of patients with large tumors with and without lymphovascular invasion and the median tumor diameter were similar. This finding indicates that lymphovascular invasion is not directly related to tumor size.

According to various research, the number of metastatic lymph nodes is significantly higher in patients with lymphovascular invasion [17, 19, 25]. We found that the median number of metastatic lymph nodes and N-ratio values were significantly higher in patients with lymphovascular invasion than in those without, which reveals that lymphovascular invasion and lymph node metastasis are directly related, and more lymph nodes are involved in those with lymphovascular invasion.

Limitations

Direct prognostic data such as survival and recurrence were not included in the study because we aimed to examine the relationship between tumor size, lymph node metastasis, and other histopathological findings that affect prognosis.

Conclusions

There is no direct relationship between tumor diameter and lymph node metastasis and N-ratio in colon adenocarcinomas, and tumor diameter does not provide reliable information about lymph node metastasis. Our findings indicate that perineural and lymphovascular invasion are not directly related to tumor diameter but may be associated with lymph node metastasis.

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Journal of Surgery and Medicine

A case of Adie’s tonic pupil

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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

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Abstract

Adie's tonic pupil, the round unilateral tonic pupil, is a neuro-ophthalmologic disorder with dilation and no light response. Although usually idiopathic, it may be associated with infection, inflammation, and postganglionic paraneoplastic nerve damage. It is called Holmes-Adie syndrome when deep tendon reflex loss accompanies Adie’s tonic pupil. The diagnosis is made by observing a miotic response after dilated pilocarpine instillation. Spontaneous recovery depends on etiological factors.

Keywords: Adie syndrome, Tonic pupil, Pilocarpine, Anisocoria

Introduction

Adie's tonic pupil (Holmes-Adie syndrome) is usually characterized by unilateral pupillary dilatation and decreased light reflex. It may be accompanied by a decrease in deep tendon reflexes [1]. Its annual incidence is 4-7/100.000, and it is more common among females in their thirties [2, 3]. While many diseases including ocular infections and inflammations, peripheral and autonomic neuropathies, paraneoplastic syndromes, toxicity, tumors, and trauma can cause tonic pupil, idiopathic cases are most encountered. The tonic response seen during convergence is more distinct than that seen during light reflex and the diagnosis is based on tonic constriction after pilocarpine instillation [4]. It is believed that Adie's tonic pupil occurs due to damage in the postganglionic parasympathetic nerves of the eye [3, 4]. We aimed to review the basic and clinical features of the subject through a case diagnosed with Adie’s tonic pupil.

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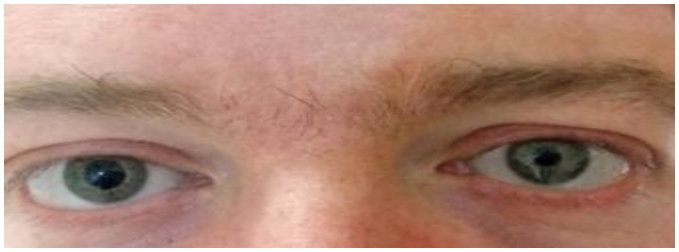
Case presentation

A 34-year-old male patient visited our neurology outpatient clinic in the past month with the complaint of blurred vision, especially when close to an object. The patient was evaluated in the ophthalmology clinic with complaints of itching and watering in his right eye two months ago, diagnosed with allergies, and prescribed betamethasone + sulfacetamide and fusidic acid drips. Neurological examination revealed a dilated right pupil (Figure 1) which was unresponsive to light and lost deep tendon reflexes.

Figure 1: Anisocoria – mydriasis on the right



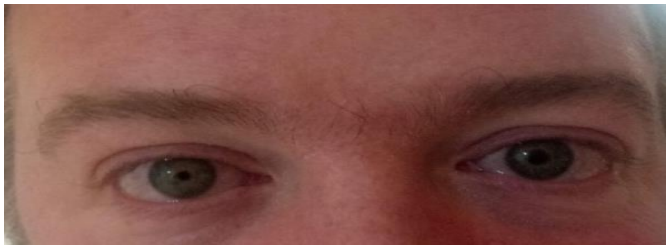
Ocular trauma, inflammation, migraine, benign episodic pupillary mydriasis, Adie's tonic pupil, oculomotor nerve paralysis, pharmacological agent use, and paraneoplastic conditions were considered as the preliminary diagnoses in the patient with anisocoria. The patient's cranial magnetic resonance (MR), cranial MR angiography and orbital MR imaging, hemogram, sedimentation, biochemistry, paraneoplastic, infectious parameters were within normal limits.

A 0.1% drop prepared by diluting 1% pilocarpine (Pilosed®) drop with ringer lactate was instilled in both eyes equally, after which the left pupil remained unchanged, but significant shrinkage was observed on the right (Figure 2). Hence, the patient was diagnosed with Adie's tonic pupil.

Clinical signs and symptoms of the patient were completely improved within two months.

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Figure 2: After 0.1% pilocarpine drop, there is myosis in the right pupil, and no change on the left.



Discussion

A difference of more than 0.1 mm between the pupil diameters is called anisocoria. In all patients with anisocoria, the shape of the pupil, its dimensions at dark and light, response to light and near stimuli, eyelid conditions, and eye movements should be evaluated. If anisocoria is more pronounced in the dark, the smaller pupil should be considered the problem and pathologies related to the sympathetic system should be investigated [5]. If the anisocoria is more prominent in a bright environment, parasympathetic system pathologies should be assessed. Unilateral, isolated anisocoria causes include ocular trauma, inflammation, Adie's tonic pupil, oculomotor nerve paralysis, pharmacological agent exposure, keratoplasty operation, paraneoplastic syndromes, syphilis, benign episodic pupillary mydriasis, migraine, and seizures [6]. In our case, Adie's tonic pupil was diagnosed due to the absence of similar complaints before this visit, no pathology in imaging studies, near-light dissociation, and response to 0.1% pilocarpine in the affected eye. Denervation hypersensitivity refers to the increased miotic response observed in the tonic eye compared to the unaffected eye when 0.1% pilocarpine solution is dropped on both. Thompson et al. suggested that cholinergic hypersensitivity is not typical but pathognomonic for a tonic pupil [7].

William et al. [8] stated that following ciliary ganglion injury, light-near dissociation develops in the iris sphincter of the tonic eye due to postganglionic parasympathetic denervation. Other causes of light-close dissociation include Argyll Robertson pupil following Herpes Zoster Ophthalmicus, aberrant degeneration of the third nerve, juvenile diabetes, myotonic dystrophy, dorsal midbrain syndrome of Parinaud, pituitary tumors, encephalitis, and chronic alcoholism [8].

Although the prognosis of Adie's tonic pupil disease is benign, cases with angle-closure glaucoma have been reported in the literature [9-10].

Conclusion

Patients with anisocoria should undergo a thorough neurological examination and other underlying diseases should be investigated with cranial MR, cranial MR angiography, and orbital MR before making the diagnosis of Adie's tonic pupil. Adie's tonic pupil is a rare disease that should be considered in patients with anisocoria.

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A case of aortic dissection presenting with a transient ischemic attack

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Abstract

Aortic dissection (AD) is the rupture of the aortic intima, separation of the tunica media and blood filling into the wall. It is an exceedingly rare life-threatening disease with a high mortality rate. The pathogenesis of AD is multifactorial and aortic diseases such as aortic dilatation, aneurysm, ectasia, arteritis, bicuspid aorta, aortic arch hypoplasia, coarctation, chromosomal abnormalities (Turner, Noonan), connective tissue disease (Marfan, Ehlers-Danlos) are well-defined risk factors for aortic dissection. Chest pain is the most common clinical presentation of AD. Cardiovascular and neurological systems are often affected. Patients with AD may also present with unexpected symptoms such as syncope, hemiparesis-hemiplegia, paraparesis-paraplegia, myocardial infarction, dysphagia, and side pain. In this article, we present a patient who presented to the emergency department with neck pain, amaurosis fugax, and hypotension, who was admitted to the neurology ward with suspicion of transient ischemic attack and diagnosed with aortic dissection.

Keywords: Aortic dissection, Transient ischemic attack, Hypotension

Introduction

Aortic dissection (AD) is the rupture of the aortic intima, separation of the tunica media and blood filling into the wall. AD, which has a high mortality rate, is a rare life-threatening disease [1]. The pathogenesis of AD is multifactorial and aortic diseases such as aortic dilatation, aneurysm, ectasia, arteritis, bicuspid aorta, aortic arch hypoplasia, coarctation, chromosomal abnormalities (Turner, Noonan), connective tissue disease (Marfan, Ehlers-Danlos) are well-defined risk factors for aortic dissection. The most widely used terminology in AD is DeBakey classification: Type I dissection starts from the ascending aorta and extends through the transverse arch to anywhere in the descending aorta. Type II starts from the ascending aorta and ends before the innominate artery. Type III starts from the left subclavian artery region and ends in the diaphragm (IIIa) or abdomen (IIIb) [2]. The Stanford classification, which is another classification used in AD, is more functional. Accordingly, aortic dissections are divided into two types. Regardless of where Type A primary tear is located, all dissections in which the ascending aorta is involved are called Type A, and distal involvement in the subclavian artery is called Type B [3].

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Chest pain is the most common clinical presentation of AD. The pain in the chest is severe, sometimes tearing, stabbing, or sharp, is sudden onset, and reaches the maximum in a brief time. Studies report that 10-55% of patients have painless aortic dissection [4]. More than one-third of the patients with AD present symptoms and signs of secondary organ involvement. Cardiovascular and neurological systems are the most involved [5]. Patients with AD may also present with unexpected symptoms such as syncope, hemiparesis-hemiplegia, paraparesis-paraplegia, myocardial infarction, dysphagia, and side pain. Studies showed that 31-39% of acute aortic dissections are initially misdiagnosed [6]. In this case report, we present a patient admitted to the emergency department with neck pain, amaurosis fugax, and hypotension, who was transferred to the neurology department with the preliminary diagnosis of a transient ischemic attack. The study aims to examine the patient diagnosed with aortic dissection by further investigations in the light of literature.

Case presentation

A 57-year-old male patient with no history of chronic diseases and trauma was admitted to the emergency department with complaints of neck pain, dizziness, hypotension, and transient visual loss in his right eye. Neurological examination of the patient in the emergency department was normal. The patient's vital signs were as follows: Blood pressure was 80/50 mmHg, fever was 36.2°C and pulse was 72/min. Electrocardiography (ECG) was compatible with early repolarization. There were no abnormal findings except for creatinine elevation in routine blood tests. The cardiac enzymes examined in the emergency department were normal. D-dimer value, chest X-ray (Figure 1), cranial tomography (Figure 2a), and cranial diffusion (Figure 2b, 2c) were normal in magnetic resonance imaging (MRI).

Figure 1: Normal chest X-ray

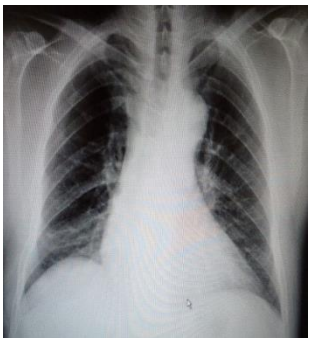


Figure 2a: Normal cranial tomography findings

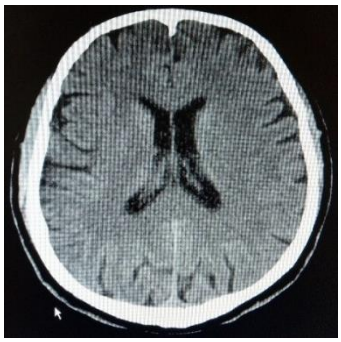


Figure 2b: Normal Diffusion-weighted magnetic resonance imaging

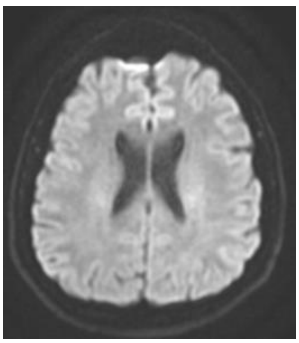
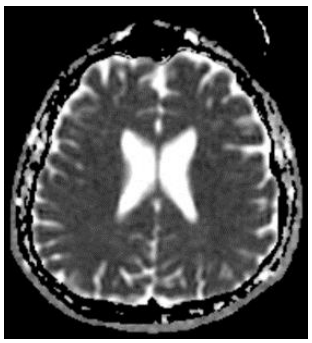
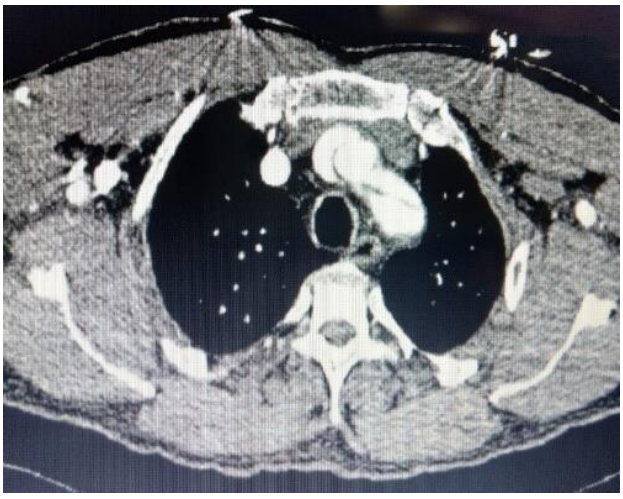


Figure 2c: Normal Apparent diffusion coefficient



The patient was hospitalized in the neurology department with a preliminary diagnosis of a transient ischemic attack. Forty milligrams of low molecular weight heparin (enoxaparin sodium) was administered twice a day, and 100 mg acetylsalicylic acid was administered once a day. The patient was hydrated with isotonic saline for hypotension. Carotid-vertebral artery Doppler ultrasonography (USG) was performed to investigate the etiology of the transient ischemic attack after admission to the neurology department. Carotid-vertebral artery Doppler USG revealed an intimal flap extending from the arcus aorta to the mid-section of the right common carotid artery (CCA), and that the thrombosed pharyngeal lumen was observed in the superior region of the intimal flap, which was compatible with a thrombosed dissection. The cardiology department was consulted to investigate the etiology of the transient ischemic attack and hypotension. The patient was then diagnosed with aortic dissection by transthoracic echocardiography (TTE). His ejection fraction was 60%. The ascending aorta was measured as 55 mm. A dissection flap was seen in the aortic arch. The patient was referred to the cardiovascular surgery department in a tertiary medical center for treatment. Thoracic computerized tomographic (CT) angiography and abdominal aortic angiography were performed at the center where the patient was referred for further examination and treatment, which revealed that the diameter of the ascending aorta was 51 mm and an intraarticular lumen dissection flap starting from proximal aorta extending to the aortic arch (Figure 3). The dissection flap was monitored along the right brachiocephalic trunk. No pathological finding was present in abdominal CT angiography. The patient was operated on by the cardiovascular surgery department with the diagnosis of aortic dissection, recovered uneventfully, and was discharged from the hospital.

Figure 3: Thoracic computed tomographic (CT) angiography: The diameter of the ascending aorta was 51 mm, and an intraarticular lumen dissection flap was observed starting from proximal aorta to the aortic arch.



Discussion

Aortic dissection is a life-threatening disease characterized by sudden chest and/or back pain. The disease is twice as common in males compared to females [7]. It should be kept in mind that aortic dissection may be painless in 10-55% of cases [5]. These cases are often associated with signs of stroke, coma or spinal cord ischemia, acute renal failure, myocardial infarction, and mesenteric ischemia [8].

Studies report that aortic dissection should be considered in patients with symptoms and findings such as back and chest pain before the stroke, syncope, hypotension, lack of pulse, and aortic regurgitation murmur [9]. The first and crucial point in the diagnosis of aortic dissection is to think of dissection. CT angiography is most used as the first diagnostic test in aortic dissection. MRI, CT angiography, and TTE have similar sensitivity and specificity in their diagnosis. Due to the high cost of these tests, access difficulties, high radiation exposure, the use of contrast material, and consequently the occurrence of adverse effects such as anaphylaxis and acute renal failure, more simple and useful biochemical tests were required in the case of suspicion of aortic dissections and the exclusion of this diagnosis [10]. Some studies indicate that serum D-dimer values may be high in aortic dissection, and D-dimer level may be a useful parameter in the exclusion of aortic dissection diagnosis [11]. Blood D-dimer levels should be evaluated within 6 hours after the onset of symptoms, especially in the exclusion of the diagnosis of aortic dissections presenting with painless, atypical clinical findings. Detection of elevated D-dimer allows patients to undergo faster imaging (CT, MRI) procedures and be referred to surgery faster, but this test has high sensitivity and low specificity. The literature review showed that CT, chest X-ray, and ECG were normal in a 66-year-old male patient who had transient ischemic attack findings in the form of weakness in the left arm during and after syncope. The patient's neurological examination was normal. Pulse rate was 45/min and arterial blood pressure was 80/60 mmHg. D-dimer value was > 4000 ng/ml (normal range <500 ng/ml). A thoracic CT angiography was performed on the patient at once and the patient was referred to surgery with the diagnosis of an ascending aortic dissection [12]. In another study involving 61 patients, blood D-dimer levels were not always high in patients with acute aortic dissection and there was no correlation between acute aortic dissection and D-dimer levels [13]. In our case, blood D-Dimer levels were normal.

There are reports of aortic dissection cases presenting with neurological symptoms and complications in the literature. In one of the case reports, an 84-year-old female patient with transient ischemic attack symptoms and hypotension in the form of recurrent aphasia episodes and right-sided weakness was reported to have aortic dissection in transesophageal echocardiography performed to investigate the etiology of transient ischemic attack and it was emphasized that acute painless aortic dissection may present with recurrent transient ischemic attack symptoms [14]. In another case report, a 73-year-old female patient presented with transient ischemic attack symptoms in the form of transient left hemiparesis and dysarthria. Carotid Doppler ultrasonography revealed CCA stenosis and mobile flaps on CCA origin and the patient was evaluated by thorax tomography and the diagnosis of thoracic aortic dissection was confirmed [15]. Like other published case reports, our case also presented with transient loss of vision in the right eye (amaurosis fugax), transient ischemic attack symptoms in the form of dizziness, and hypotension. It was highlighted that aortic dissections should be considered in patients with transient ischemic attack symptoms without chest or back pain.

Conclusion

Cerebral ischemic events can be observed in 5-10% of cases with aortic dissection. The most important factor in the diagnosis of acute aortic dissection is considering the possibility of dissection. In our case, there were no typical findings of aortic dissection. Therefore, it is important to keep in mind the diagnosis of aortic dissection in patients presenting with unexpected symptoms such as hypotension, neck pain, and focal neurological deficits to the emergency department and evaluate patients with appropriate imaging techniques. The mortality rate could be significantly reduced by providing early treatment with a rapid and accurate diagnosis process.

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