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A prospective study on the relationship between COVID-19 disease progress and cardiovascular damage

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Abstract

Background/Aim: Covid-19 is a new coronavirus disease with high mortality that has reached all parts of the world. This study aimed to prospectively compare individual characteristics, echocardiographic findings, and laboratory findings in patients with Covid-19 according to the need for intensive care unit (ICU) admission and mortality.

Methods: In this single-center prospective cohort study, patients hospitalized with the diagnosis of Covid-19 between June and November 2020 were examined in terms of echocardiographic and laboratory results. Early in-hospital findings that might affect mortality, cardiac injury and thrombotic complications were evaluated and compared.

Results: A total of 214 patients who were hospitalized due to Covid-19 were included in our study, 80 (37.3%) of which needed hospitalization in the ICU and 134 (62.6%) of which did not. The mean ages of patients treated in the ICU unit and the ward were 69.5 (57.5-80.5) years and 40 (29-58) years, respectively ($P<0.001$). Among patients hospitalized in the ICU, mean Troponin T on Day 1 (27.12 ng / L, range: 10.48-70.51, $P<0.001$), mean Troponin T on Day 3 (31.5ng / L, range: 10.24 - 114.5, $P<0.001$) and mean D-dimer (2.84ng / L, range: 1.1-8.22, $P<0.001$) levels of those who died were significantly higher compared to survivors. These parameters were important markers of mortality along with right ventricular end-diastolic diameter (RVDD) (3.3 cm (2.8-3.7) $P<001$).

Conclusion: While cardiac damage and high D-dimer values suggest the possibility of pulmonary microembolism in those who need ICU hospitalization, the relationship between RVDD and mortality supports the possibility of pulmonary embolism.

Keywords: Covid-19, D-dimer, Cardiac damage, ICU, RVDD

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Introduction

Covid-19 disease caused by the SARS2-CoV-2 viral infection that started in Wuhan in December 2019 was declared a pandemic by the World Health Organization (WHO) [1]. The SARS-CoV-2 is an enveloped virus of the Coronavirus (CoV) family, with a characteristic genome composed of RNA. Its clinical severity may range from asymptomatic to symptomatic (including fever, cough, shortness of breath, malaise, muscle pain and diarrhea). More importantly, it can cause a disease of the respiratory tract which may progress to acute respiratory distress syndrome (ARDS) and fatal organ failure [2]. The disease has greater infectivity than influenza, in addition to its higher mortality rate. The high infectivity and relatively high rate of serious complications have caused Covid-19 to become a serious public health threat worldwide [3, 4]. The disease may also cause arrhythmia through some proinflammatory mediators [5]. Despite cardiac manifestations being reported in the literature, mortality and complications are primarily related to respiratory involvement in patients with Covid-19 [6]. Several studies have shown that, along with respiratory tract defects, heart damage is observed in 20-30% of hospitalized patients and may be associated with mortality in up to 40% [7-9].

In the present study, the effects of echocardiographic examination, cardiac injury markers and laboratory parameters on mortality were investigated prospectively among hospitalized Covid-19 patients, with analyses based on comparing patients hospitalized in the ICU and the ward, and respective survival and mortality rates.

Materials and methods

Study population

Patients who presented to Şanlıurfa Mehmet Akif İnan Training and Research Hospital with Covid-19 symptoms and were hospitalized after diagnostic confirmation with positive real-time reverse transcription polymerase chain reaction (RT-PCR) between June-November 2020 were included in this prospective study. They were assessed in two groups according to intensive care requirement. The echocardiographic examination and laboratory findings of patients who required admission to the intensive care unit (ICU) (n = 80) and those who were hospitalized without need of ICU admission (n = 134) were evaluated and compared. We also compared patient characteristics based on fatal disease progression.

All hospitalized patients received routine medical treatment, in-line with WHO recommendations as per the current treatment guidelines prepared by the Turkish Ministry of Health. Patients with chronic renal or heart failure, acute coronary syndrome, coronary artery disease and a history of previous cerebrovascular events were excluded from the study.

Demographic characteristics (age, gender), smoking status, and hypertension (HT) and diabetes mellitus (DM) histories were recorded as part of patient history. Laboratory findings, including glucose, urea, creatinine, sodium, potassium, calcium, D-dimer, procalcitonin, fibrinogen, ferritin, CKMB, hemoglobin, lymphocyte, neutrophil, and troponin (cTnT) were measured from blood samples obtained on days 1 and 3 of hospitalization. cTnT values being above the 99th percentile was

considered a marker of newly developed cardiac injury, regardless of echocardiographic findings. To validate Covid-19, a Viral nucleic acid Kit was used to extract nucleic acids from clinical samples, in accordance with the kit instructions. The study was approved by the Harran university Ethics Committee (date:27.04.2020 and number: HRU/20.08.23) and carried out in accordance with the Helsinki Declaration.

Echocardiographic evaluation

All patients included in the study underwent echocardiography in isolated wards and ICUs. Examinations in the parasternal long-axis view and the apical 4-chamber plane were conducted with patients in the left lateral decubitus position. A Philips EPIQ 7 system (Philips EPIQ7, Bothell, WA, USA) 3.5 MHz transducer was used for echocardiographic evaluation, during which two-dimensional instant and color Doppler evaluations were performed with standard techniques. Left atrium (LA) size, left ventricle (LV) end-diastolic diameter (LVDD) and LV end-systolic diameter (LVSD), right ventricular end-diastolic diameter (RVDD) were measured using the M-mode method. Pulmonary arterial pressure (PAB) was measured from the tricuspid valve. LV ejection fraction (LVEF) was calculated using Simpson's method.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used for normality check. Data are presented as median (1st quartile – 3rd quartile) for continuous variables, and as frequency (percentage) for categorical variables. Non-normally distributed variables were analyzed with Mann-Whitney U test, and categorical variables were analyzed with the Pearson's chi-square test. Logistic regression analysis (forward conditional method) was performed to identify the risk factors of mortality and ICU requirement. Variables that were statistically significant in univariate analyses were included in the regression models. Two-tailed P-values of less than 0.05 were considered statistically significant.

Results

Gender, age, WBC, hemoglobin, glucose, sodium, calcium, creatinine (1st day), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, CRP, INR, creatine kinase-MB (CKMB) (1st and 3rd day), troponin (1st and 3rd day), ferritin, D-dimer, procalcitonin, ejection fraction percentage (EF%), PABs, fever, cough, diarrhea, dyspnea, myalgia, fatigue, hypertension, diabetes mellitus were significantly associated with ICU need (Table 1).

Age, ICU need, WBC, hemoglobin, glucose, sodium, creatinine (1st and 3rd day), AST, albumin, CKMB (1st and 3rd day), troponin (1st and 3rd day), ferritin, D-dimer, procalcitonin, EF%, RVDD, PABs, dyspnea, diabetes mellitus, and cancer were significantly associated with mortality (Table 2).

Table 1: Clinical variables compared with respect to ICU need

| | ICU need | | |
	Absent	Present	P-value
Gender			
Male	87 (67.97%)	41 (32.03%)	0.048
Female	47 (54.65%)	39 (45.35%)	
Age	40 (29 - 58)	69.5 (57.5 - 80.5)	<0.001
White blood cell	7.38 (5.89 - 10.72)	11.8 (8.69 - 15.93)	<0.001
Hemoglobin	14.75 (13.4 - 15.7)	12.55 (10.7 - 14)	<0.001
Platelet	255 (195 - 289)	239 (185.5 - 281.5)	0.247
Glucose	112 (99 - 144)	163.5 (123.5 - 225)	<0.001
Sodium	140 (137 - 141)	137 (133 - 140)	<0.001
Potassium	4.39 (4.1 - 4.68)	4.6 (4.13 - 5.09)	0.015
Calcium	9.11 (8.73 - 9.44)	8.6 (8.18 - 8.9)	<0.001
Creatinine (1st day)	0.93 (0.77 - 1.08)	1.1 (0.78 - 1.67)	0.002
Creatinine (3rd day)	0.9 (0.77 - 1)	1 (0.68 - 1.5)	0.208
ALT	17.8 (11.4 - 26.4)	24 (12.3 - 39.5)	0.041
AST	20.1 (15 - 25.9)	30.85 (20.5 - 49.5)	<0.001
Albumin	43.93 (39.16 - 46.29)	31.92 (30 - 35.92)	<0.001
CRP	11.16 (2.85 - 41.33)	94.99 (35.8 - 188.33)	<0.001
INR	1.08 (1.02 - 1.15)	1.1 (1.05 - 1.3)	0.002
CKMB (1st day)	1.19 (0.83 - 1.99)	1.72 (0.95 - 2.81)	0.014
CKMB (3rd day)	1.5 (1 - 2.5)	2.17 (1.3 - 3.3)	0.001
Troponin (1st day)	3 (3 - 5.14)	27.12 (10.48 - 70.51)	<0.001
Troponin (3rd day)	3.39 (3 - 6.23)	31.5 (10.24 - 114.5)	<0.001
Fibrinogen	3 (2 - 4)	3.2 (2.3 - 4.8)	0.077
Ferritin	78 (56 - 133)	536 (213 - 1256)	<0.001
Procalcitonin	0.13 (0.04 - 0.27)	0.4 (0.15 - 1.2)	<0.001
D-dimer	0.23 (0.14 - 0.5)	1.55 (0.61 - 4)	<0.001
EF%	60 (55 - 65)	55 (50 - 60)	<0.001
LA	3.55 (3.4 - 3.7)	3.6 (3.45 - 3.7)	0.390
LVDD	4.5 (4.4 - 4.7)	4.6 (4.5 - 4.7)	0.071
RVDD	2.8 (2.5 - 3)	2.6 (2.5 - 3.1)	0.212
PABs	25 (24 - 32)	35 (29 - 45)	<0.001
Fever	73 (53.68%)	63 (46.32%)	<0.001
Cough	102 (57.95%)	74 (42.05%)	0.002
Diarrhea	3 (16.67%)	15 (83.33%)	<0.001
Chest pain	9 (45.00%)	11 (55.00%)	0.087
Dyspnea	43 (36.75%)	74 (63.25%)	<0.001
Myalgia	30 (32.97%)	61 (67.03%)	<0.001
Fatigue	34 (35.79%)	61 (64.21%)	<0.001
Headache	15 (71.43%)	6 (28.57%)	0.379
Sore throat	32 (71.11%)	13 (28.89%)	0.185
Hypertension	21 (38.18%)	34 (61.82%)	<0.001
Diabetes mellitus	16 (30.19%)	37 (69.81%)	<0.001
Cancer	5 (45.54%)	6 (54.55%)	0.227
Smoking	35 (62.50%)	21 (37.5%)	0.983

Data are given as median (1st quartile – 3rd quartile) for continuous variables, and frequency (percentage) for categorical variables.

Table 2: Clinical variables compared among patients who survived and those who died

| | Result | | |
	Survived	Died	P-value
Gender			
Male	120 (93.75%)	8 (6.25%)	0.596
Female	79 (91.86%)	7 (8.14%)	
Age	53.00 (33.00 - 69.00)	62.00 (51.00 - 79.00)	0.044
ICU need			
Absent	134 (100.0)	0 (0%)	<0.001
Present	65 (81.25%)	15 (18.75%)	
White blood cell	8.79 (6.28 - 11.99)	14.12 (7.7 - 18)	0.014
Hemoglobin	14.2 (12.5 - 15.4)	12 (10.3 - 12.8)	0.001
Platelet	245 (194 - 285)	232 (167 - 330)	0.700
Glucose	120 (101 - 174)	173 (127 - 291)	0.003
Sodium	139 (136 - 141)	134 (130 - 138)	0.002
Potassium	4.45 (4.1 - 4.74)	4.7 (4.21 - 5.6)	0.095
Calcium	8.93 (8.5 - 9.3)	8.63 (8.2 - 9.2)	0.117
Creatinine (1st day)	0.95 (0.77 - 1.11)	1.5 (0.89 - 1.8)	0.003
Creatinine (3rd day)	0.9 (0.75 - 1.07)	1.26 (1 - 2.15)	0.002
ALT	18.5 (11.4 - 31)	21 (14 - 64)	0.296
AST	22.1 (16 - 32.5)	38 (21 - 69.7)	0.003
Albumin	40.1 (33 - 45.09)	32.9 (27.25 - 37)	0.001
CRP	23.18 (4.04 - 90.01)	73 (5.21 - 182.67)	0.065
INR	1.1 (1.02 - 1.2)	1.2 (0.93 - 1.8)	0.297
CKMB (1st day)	1.23 (0.84 - 2.17)	2.8 (1.6 - 4.08)	0.006
CKMB (3rd day)	1.7 (1 - 3)	3.2 (2 - 5)	0.003
Troponin (1st day)	4.7 (3 - 14.6)	46.1 (26.57 - 162.2)	<0.001
Troponin (3rd day)	6 (3 - 20)	98 (29 - 145)	<0.001
Fibrinogen	3.05 (2 - 4.4)	2.9 (1.76 - 3.4)	0.092
Ferritin	98.5 (67 - 353)	456 (138 - 936)	0.003
Procalcitonin	0.16 (0.05 - 0.44)	0.45 (0.16 - 4.1)	0.003
D-dimer	0.42 (0.18 - 1.3)	2.84 (1.1 - 8.22)	<0.001
EF%	60 (55 - 60)	50 (45 - 60)	0.008
LA	3.6 (3.4 - 3.7)	3.6 (3.4 - 3.9)	0.763
LVDD	4.5 (4.4 - 4.7)	4.5 (4.4 - 4.5)	0.063
RVDD	2.7 (2.5 - 3)	3.3 (2.8 - 3.7)	<0.001
PABs	27 (24 - 35)	45 (34 - 50)	<0.001
Fever	125 (91.91%)	11 (8.09%)	0.414
Cough	162 (92.05%)	14 (7.95%)	0.244
Diarrhea	17 (94.44%)	1 (5.56%)	0.801
Chest pain	17 (85.00%)	3 (15.00%)	0.142
Dyspnea	105 (89.74%)	12 (10.26%)	0.041
Myalgia	82 (90.11%)	9 (9.89%)	0.156
Fatigue	88 (92.63%)	7 (7.37%)	0.854
Headache	20 (95.24%)	1 (4.76%)	0.671
Sore throat	42 (93.33%)	3 (6.67%)	0.919
Hypertension	48 (87.27%)	7 (12.73%)	0.054
Diabetes mellitus	45 (84.91%)	8 (15.09%)	0.008
Cancer	7 (63.64%)	4 (36.36%)	<0.001
Smoking	52 (92.86%)	4 (7.14%)	0.964

Data are given as median (1st quartile – 3rd quartile) for continuous variables, and frequency (percentage) for categorical variables.

We performed Cox regression analysis to determine significant factors associated with mortality. Sodium level (OR: 0.806, 95% CI: 0.703-0.924, P=0.002), AST level (OR: 1.015, 95% CI: 1.004-1.026, P=0.007), and RVDD (OR: 19.662, 95% CI: 5.371-71.971, P<0.001) were associated with mortality, while other variables included in the model, namely, age (P=0.281), WBC (P=0.485), hemoglobin (P=0.507), glucose (P=0.210), 1st day creatinine (P=0.278), 1st day CKMB (P=0.665), 1st day troponin (P=0.870), ferritin (P=0.742), D-dimer (P=0.090), procalcitonin (P=0.074), dyspnea (P=0.205), diabetes mellitus (P=0.617), PAB (P=0.874), cancer (P=0.178), ejection fraction (P=0.374), and ICU need (P=0.994) were not (Table 3).

Table 3: Significant factors of death, multiple logistic regression analysis (Forward conditional, step 5)

	β coefficient	Standard Error	Wald	P-value	Exp(β)	95.0% CI for Exp(β)	
Sodium	-0,216	0.070	9.541	0.002	0.806	0.703	0.924
AST	0,015	0.006	7.291	0.007	1.015	1.004	1.026
RVDD	2,979	0.662	20.243	<0.001	19.662	5.371	71.971
Constant	-1.843	8.730	3.834	0.050			

CI: Confidence Interval, Dependent Variable: Death, Nagelkerke R^2=0.464

Multiple logistic regression analysis revealed that age (OR: 1.072, 95% CI: 1.039-1.106, P<0.001), AST level (OR: 1.049, 95% CI: 1.019-1.080, P=0.001), 1st day troponin level (OR: 1.018, 95% CI: 1.004-1.032, P=0.013), dyspnea (OR: 9.762, 95% CI: 2.871-33.196, P<0.001), fatigue (OR: 4.727, 95% CI: 1.828-12.225, P=0.001) were associated with ICU need, while gender (P=0.808), WBC (P=0.265), hemoglobin (P=0.439), glucose (P=0.683), sodium (P=0.190), calcium (P=0.051), ALT (P=0.459), albumin (P=0.074), CRP (P=0.093), 1st day CKBM (P=0.557), ferritin (P=0.894), D-dimer (P=0.613), procalcitonin (P=0.697), fever (P=0.989), cough (P=0.168), headache (P=0.844), hypertension (P=0.540), and diabetes mellitus (P=0.537) were not (Table 4).

Table 4: Significant factors of ICU need, multiple logistic regression analysis (Forward conditional, step 10)

	β coefficient	Standard Error	Wald	P-value	Exp(β)	95.0% CI for Exp(β)	
Age	0.069	0.016	19.124	<0.001	1.072	1.039	1.106
AST	0.048	0.015	10.355	0.001	1.049	1.019	1.080
1st day troponin	0.018	0.007	6.116	0.013	1.018	1.004	1.032
Dyspnea	2.279	0.624	13.313	<0.001	9.762	2.871	33.196
Fatigue	1.553	0.485	10.265	0.001	4.727	1.828	12.225
Constant	-8.721	1.381	39.861	<0.001			

CI: Confidence Interval, Dependent Variable: ICU need, Nagelkerke R^2=0.744

Discussion

This study shows that mortality among hospitalized patients with Covid-19 was significantly related to cTnT, RVDD, and especially D-dimer (as shown by logistic regression). In previous studies, high troponin levels and myocardial damage were identified with infection, in addition to varying degrees of electrocardiographic and echocardiographic abnormalities [8, 10]. Such relationships have become more remarkable with the increasing number of cases all over the world. As of November 21, while there was a total of more than 440,000 Covid-19 cases in Turkey, and more than 58 million laboratory-confirmed cases around the world.

Severe respiratory distress (as in ARDS) is considered the main cause of death in Covid-19; therefore, severe pneumonia was associated with mortality regardless of admission to the intensive care unit, or the need of mechanical ventilation [11]. Co-morbidities, such as advanced age, diabetes, hypertension, and coronary artery disease, are well established as factors that

increase the possibility of being infected with Covid-19 and related mortality [12]. Similarly, in our study, advanced age, diabetes, and hypertension were risk factors in terms of ICU requirement, but this risk was not found in smokers. Significant differences in age, diabetes, hypertension, cTnT, D-dimer, ferritin and procalcitonin in patients in need of ICU (compared to those without) suggests that factors other than primary lung infection may also contribute to disease progression in these patients. While 7.2% of the patients hospitalized with the diagnosis of Covid-19 developed acute heart injury, overall, cardiac injury was observed at a higher frequency in patients who were hospitalized in the ICU compared to those who were not (22.2%) [13]. Although it was revealed that there was a strong relationship between ICU need and cardiac injury, a meta-analysis showed that high cTnT is associated with cardiac injury [7]. In another meta-analysis including 341 patients, increased cTnT levels were associated with fatal Covid-19 infection [14]. In a study examining 191 patients, hs-cTnI (high-sensitivity Troponin I) increased in more than half of the hospitalized patients who died due to Covid-19 disease. In these patients, hs-cTnI levels were higher than 28pg/ml in 46%, whereas this rate was around 1% in survivors, indicating a considerable association between hs-cTnI levels and mortality [15]. This was further exemplified by a study evaluating 416 patients, among which 19.7% had cardiac injury. The requirement for invasive or non-invasive ventilation was observed to a greater degree in these patients, especially those with high cTnT values [16]. In our study, a significant correlation was observed between cardiac damage and clinical disease severity. The significant correlation between ICU requirement decreased LVEF and increased cTnT on days 1 and 3 suggests a role of cardiac injury in ICU need. A single-center study with a similar design to ours reported cardiac injury in 19% of patients hospitalized with Covid-19; moreover, cardiac damage was closely associated with in-hospital mortality [7]. In our study, the significant relationship between ICU need and cTnT levels (as a marker of cardiac damage) on both the first and third days supports this hypothesis and provides further evidence for the notion that a close relationship between cardiac damage and mortality exists.

There was a significant relationship between D-dimer, ferritin and procalcitonin levels and the need for ICU admission. In a similar study, the finding that D-dimer levels were greater than 500 ng/ml in patients who died (compared to survivors) was put forward as an independent indicator of the prothrombotic process [17]. Systemic microvascular thrombosis is common in critical patients infected with Covid-19 and has been associated with death [18,19]. In addition, infection-induced coagulopathy and hyperfibrinolysis are common in severe cases [20]. In our study, high D-dimer levels, in addition to indicating that the course of the disease would be critical, were associated with mortality. Again, in a retrospective study in which 343 patients were included, D-dimer > 2.0 n/ml was associated with in-hospital mortality in patients infected with Covid-19, and it was shown that D-dimer was an effective marker in determining treatment approach [21]. The relationship between pulmonary embolism and RVDD has been previously shown [22]. In our study, the significant increase in right ventricular pressures (PABs) and right ventricular diameters (RVDD) together with the elevation of D-dimer in patients who required ICU care supports the presence of a prothrombotic effect which may lead to pulmonary embolism. The observation of a significant relationship between increased RVDD and mortality in patients needing ICU treatment supports this notion [23]. The increase in RVDD values in our study may have caused an increase in cTnT, which possibly led to the deterioration in right ventricular functions secondary to pulmonary embolism. The relationships between mortality and parameters such as RVDD, PAB and D-dimer may suggest that mortality due to Covid-19 may develop in relation with microvascular thrombosis. Unlike many studies in the literature, echocardiographic findings in our prospective study are important in terms of showing microembolic complications in Covid-19 infection, despite the use of antiaggregant and antithrombotic therapy.

Limitations

Our study has some limitations. First, the research was conducted in a single center and the number of patients, especially in the mortality group, was low. Second, the current state of routine practice (due to Covid-19) prevented the evaluation of a greater number of echocardiographic analyses and longitudinal follow-up. Third, brain natriuretic peptide levels could not be evaluated.

Conclusion

While significant relationships were found between various parameters, co-morbid factors and the requirement of ICU or the development of mortality in patients with Covid-19, regression analyses demonstrated that significant factors were much fewer than suggested by univariate analyses. Of note, interestingly, smoking was not a factor that increased ICU admission or death, a finding that has been mirrored in some studies. Prospective data obtained from our study support the significant relationship between mortality and the levels of cTnT, RVDD and D-dimer, and show that these may indicate the formation of end-stage cardiac injury, microvascular thrombosis and pulmonary embolism in patients admitted to the ICU. The RVDD and PAB values might be valuable markers that could predict mortality, which warrants further studies on this subject to elucidate these relationships and aid physicians in the management of patients with Covid-19.

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Short-term clinical and radiological outcomes of treatment of acromioclavicular joint dislocations with the TightRope technique

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Abstract

Background/Aim: High-grade acromioclavicular joint injuries are usually treated surgically. However, there is still no consensus on which technique should be performed. We investigated the short-term clinical and radiological outcomes of the patients treated with the TightRope technique.

Methods: In this retrospective cohort study, 15 patients (13 males and 2 females) who had an acromioclavicular joint injury and were treated with the TightRope technique between October 2015 and May 2019 were evaluated. The patients who had Rockwood type III (1 patient), type IV (8 patients), and type V (6 patients) injuries and had been followed up for at least 1 year were included in the study. At the final visits, the patients were evaluated functionally with VAS, DASH, and Constant scores, as well as radiologically by measuring the coracoclavicular distance on bilateral shoulder AP X-rays.

Results: The mean duration of follow-up was 25.2 (5.6) months. Mean time to surgery was 3.0 (2.2) days and mean time to return to work was 8.8 (1.7) weeks. The coracoclavicular distance was 11.6 (2.1) mm on the affected side and 10.2 (0.8) mm in the other shoulder. Mean VAS, DASH, and Constant scores at the final visit were 1, 10, and 92, respectively.

Conclusion: Use of the TightRope technique for the treatment of acromioclavicular dislocations might be effective like other methods that contribute to early regaining of range of motion of the shoulder joint, in addition to reduction of the dislocation.

Keywords: Acromioclavicular Joint, TightRope Technique, Endobutton, Ligament Reconstruction

Introduction

Several procedures for the surgical treatment of acromioclavicular (AC) joint injuries have been reported in the literature, including stabilization with reinforced sutures, Kirschner (K) wire, hook plates or Bosworth screws, and reconstruction with an allograft or autograft, although none has become the gold standard [1,2].

The disadvantage of coracoclavicular screw fixation is that since rotational movement of the clavicle will be limited together with abduction of the shoulder, the implant will need to be removed after a short period [3, 4]. The most important disadvantage of the hook plate technique is the necessity of removal of the plate and narrowing of the subacromial space [4, 5]. The TightRope (Arthrex, Naples, FL, USA) technique is designed for syndesmosis injuries of the ankles and used for treatment of AC joint dislocations as well.

The objective of our study was to evaluate the short-term clinical and radiological outcomes of patients with acromioclavicular separation (ACS) who underwent surgery with the TightRope technique.

Materials and methods

This study followed the principles of the Helsinki Declaration and was approved by Ankara City Hospital Ethics and Research Committee (Date: 26/02/2020, Decision no: 72300690-799). Written informed consent was obtained from the patient whose images were presented in the study. Twenty-two patients who were diagnosed with AC joint dislocation and received surgical treatment with the TightRope technique between October 2015 and May 2019 were evaluated retrospectively. The inclusion criteria for the study were as follows: Age >18 years, acute AC joint dislocation <3 weeks, having Rockwood types III, IV, or V injuries, and having been followed up for at least 1 year. Five patients who had an ipsilateral upper extremity injury and/or a history of previous shoulder surgery and 2 patients who were lost to follow-up were excluded from the study. A total of 15 patients were included.

Of our patients, 86.7% (n=13) were male and 13.3% (n=2) female. Ten patients had right-sided and 5 had left-sided ACS. One (6.6%) had Rockwood type III, 8 (52.8%) type IV, and 6 (39.6%) type V ACS. Twelve patients had trauma due to falls and 3 had been in a vehicle crash. At the final visits, the patients were evaluated functionally with VAS, DASH, and Constant scores, as well as radiologically by measuring the coracoclavicular distance on bilateral shoulder AP X-rays. Coracoclavicular distances in the treated and healthy shoulders were evaluated on standard shoulder AP X-rays that were taken at a right angle from 1-meter distance.

Surgical technique

The patients were prepared in the lounge position under general anesthesia. A mini-oblique incision extending from the clavicle towards the coronoid process was performed. After the clavicle and the coronoid process were reached, a K wire (thickness 1.6 mm) was sent from the distal clavicle towards the coronoid process, and then clavicular and coronoid tunnels were created using a 4.5-mm drill on the K wire (Figure 1). With aid of transport sutures, the AC joints were reduced in such a way that

one of the implants was located under the coronoid process and the other over the clavicle, and the threads were then tied over the clavicle (Figure 2). All patients were treated with the same method (Figure 3). Shoulder straps were applied to the patients during the first week. All our patients' passive shoulder joint movements commenced after one week. All patients were allowed to do active exercises after 6 weeks and weightlifting, pushing, and pulling movements after 10 weeks.

Figure 1: Tunneling through the clavicle and coronoid process

Figure 2: Passing the Tight Rope system through the tunnels via the carrier suture

Figure 3: 29-year-old male patient a. Preoperative, b. Postoperative 1st day, c. Postoperative 1st year radiographs
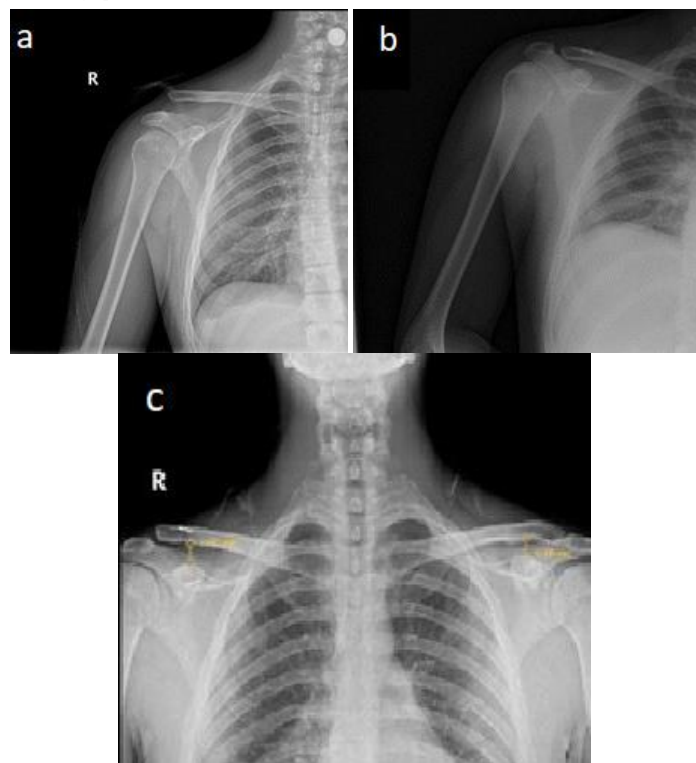
Statistical analysis

Conformity to normal distribution of the continuous variables obtained from the 15 patients included in the study, including age, time to surgery, and distance measurements, was determined by the Shapiro–Wilk test and graphical methods. For describing the variables, mean (standard deviation) and median (min, max) were used. Categorical variables like gender and side were presented as number (percentage) [n (%)].

The level of statistical significance was set at $P<0.05$. Statistical analyses were performed with IBM SPSS Statistics 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

The demographic data of our patients are shown in Table 1. The mean duration of follow-up was 25.2 (5.6) months. Mean

time to surgery was 3.0 (2.2) days and mean time to return to work was 8.8 (1.7) weeks. The coracoclavicular distance was 11.6 (2.1) mm on the affected side and 10.2 (0.8) mm in the other shoulder (Table 1). Mean VAS, DASH, and Constant scores after surgery were 1, 10, and 92, respectively (Table 2). Only 1 (6.6%) patient developed implant failure on postoperative day 10, and that patient refused a second surgical procedure.

The preoperative and postoperative VAS, DASH, and Constant scores were significantly different (P<0.001). VAS and DASH scores decreased postoperatively, whereas Constant score increased (Table 2).

Table 1: Demographic information

Variable	Mean(SD)	Median (min;max)	
Age	34.8	33.0 (21.0; 54.0)	
Rockwood classification	4.4 (0.6)	4.0 (3.0; 5.0)	
Waiting time for surgery	3.0 (2.2)	2.0 (1.0; 8.0)	
Time to return to work	8.8 (1.7)	8.0 (6.0; 12.0)	
Follow-up period	25.2 (5.6)	20.0 (14.0; 32.0)	
CC distances			
Affected side	11.6 (2.1)	10,8 (9.0; 22.0)	
Other side	10.2 (0.8)	9.8 (9.0; 12.0)	
	n (%)		n (%)
Gender		ASA	
Male	13 (86.7%)	1	8 (53.3%)
Female	2 (13.3%)	2	7 (46.7%)
Source of the trauma		Comorbidity	
Fall	12 (79.2%)	No	13 (86.7%)
Traffic accidents	3 (20.8%)	DM	1 (6.6%)
Complication		HT	1 (6.6%)
No	14 (93.4%)		
Yes	1 (6.6%)		

CC: Coracoclavicular, ASA: American society of anesthesiologists score, DM: Diabetes mellitus, HT: Hypertension

Table 2: Evaluation of functional scores preoperative and in the final follow-up

	Preoperative [n=15] Median (min; max)	Last Checkup [n=15] Median (min; max)	Test Z	Statistics P-value
VAS Score	6.2 (4.0; 7.0)	1.0 (0.0; 3.0)	3.632	<0.001
DASH Score	24.0. (18.0; 28.0)	10.0 (0.0; 15.0)	3.510	<0.001
Constant Score	33 (27.0;58.0)	92.0 (64.0; 100.0)	3.218	<0.001

VAS: Visual analog scale, DASH: Disabilities of the arm shoulder and hand

Discussion

The TightRope technique is a minimally invasive treatment option with a low complication rate and favorable short-term clinical outcomes in patients with acute ACS.

Walz et al. [6] reported that the TightRope system stabilized the AC joint, restored function and led to stronger fixation compared to natural ligaments. Cadaver studies have shown that the final load for impairment of the AC joint is approximately 500-700 Newtons (N) and that the load for impairment of the TightRope system is more than 1400 N [7, 8]. In a study by Jensen et al. in which they compared the hook plate and TightRope techniques, they reported that the CC distance changed less in the TightRope system during loading and resting [9]. Stein et al. [10] found that the CC distance after hook plate application was higher than after the use of TightRope system. In a study by Hemmann et al. [11], in which they applied hook plates, they reported the CC distance lower than 5 mm in 80.3%, between 5 and 10 mm in 14.3%, and higher than 10 mm in 5.3% of the patients. In our study, except for in 1 (6.6%) patient, the CC distance was not 5 mm greater than that in the contralateral shoulder.

Another important advantage of the TightRope system is that, thanks to the very low profile, a second surgical procedure is not necessary for removal of the implant. Following surgical treatment of ACS, complications including chronic shoulder pain, wound site infection, delayed wound healing, arthritis,

neurological injuries, clavicular erosion, and fixation failure may be observed. The most significant disadvantages of K wire fixation include loosening and migration of the implant and pin bottom infections. Although hook plates provide vertical, horizontal, and rotational stability, they have some disadvantages including subacromial impingement, subacromial erosion, osteolysis, acromial fractures, and rotator cuff arthropathy [12]. Although such complications are uncommon in the TightRope system, its most significant disadvantage is suture ruptures due to tunnel malposition [13, 14]. In our study, 1 patient developed implant failure due to excessive anterior approach of the coronoid tunnel. None of the patients had infection or other problems at the wound site.

In a study by Pauly et al. [15] in which they used the TightRope system, they reported a mean Constant score of 94.3. Darabos et al. [16] reported similar radiological and clinical outcomes in patients with Rockwood type III ACS among which they compared Bosworth screws with the TightRope system. Hemmann et al. [11] reported a mean DASH score of 5.6 (1) and Constant score of 90.0 (1.4) in a case series of patients who received hook plates. In our study, the mean DASH score was 10 and Constant score was 92. We found these values to be a favorable clinical outcome consistent with the studies conducted by Rosslenbroich et al. [17] with MINAR (mean Constant score: 94.7) or by Scheibel et al. [18] with the double TightRope technique (mean Constant score: 91.5).

Limitations

The retrospective nature of our study and the sparse number of patients are the two main limitations. Another limitation was the short follow-up period. In addition, Constant score is a general clinical evaluation test for the shoulder and is not specific to the AC joint. This may theoretically have influenced the results. The lack of a control group treated with a different method is a further limitation of our study.

We believe that the existence of a control group treated with a different method, longer follow-up periods and a study to be conducted with a larger number of patients will provide additional contributions to literature.

Conclusions

Use of the TightRope technique for treatment of acromioclavicular dislocations might be an effective method like other methods that contribute to early regaining of range of motion of the shoulder joint, in addition to reduction of the dislocation.

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Are the collagen types and density in the wound healed after midline and transverse laparotomy different? An experimental study in mice

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Abstract

Background/Aim: Whether midline or transverse incision is superior in laparotomy is still controversial. The aim of this study was to investigate the total collagen amounts in wound healing after midline and transverse incisions and reveal whether there was a difference between these two laparotomy techniques.

Methods: Twenty-four BALB/c mice were randomly divided into three groups (control, midline, and transverse groups). Mice were sacrificed 28 days after the surgical procedures. The samples were examined histochemically in terms of total collagen density, Type I and Type III collagen rate and maturation index.

Results: Total collagen density, Type I collagen rate and maturation index were slightly insignificantly higher and Type III collagen rate was insignificantly lower in the transverse incision group compared to the midline group (*P*=0.486, *P*=0.541, *P*=0.336 and *P*=0.541, respectively).

Conclusion: The total collagen density, Tip I and Tip III collagen amounts, and maturation index of wounds healed after transverse and midline laparotomy are similar according to this experimental model.

Keywords: Laparotomy, Collagen, Wound healing, Maturation index

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Introduction

Although laparoscopic procedures are increasingly used in abdominal surgeries, laparotomy procedures are still practiced frequently. Incisional hernias remain a problem for surgeons, with an incidence of 9% to 19% after laparotomy [1]. Although discussions about the ideal laparotomy closure technique are as important as the visceral surgery itself, a conclusion has not been made regarding the optimal suture material or the suture technique [1, 2]. It has been emphasized in many studies that transverse incisions are more advantageous in many aspects (e.g., pain, respiratory complications, incisional hernia risk, and early discharge and return to work) compared to midline incisions, however, midline incision is still the most preferred technique [3-5]. This is because a midline incision can be performed quickly and easily, and it can provide a wider surgical area by extending up and down depending on the need.

In the literature, there are many randomized controlled trials and meta-analyses comparing midline and transverse laparotomy procedures in clinical practice [6-9]. Although laparotomy closure techniques and suture materials are known to affect the tensile strength of the wound and the incidence of incisional hernia after laparotomy, whether the collagen content and collagen subtypes have any role in this effect have not been evaluated.

Type I and Type III collagen formations in the remodeling phase have a critical role on wound healing [10]. During scar formation, the first collagen type to occur is Type III collagen, with low tensile strength. The amount of Type III collagen, which is initially seen at a rate of 80%, decreases gradually during scar formation and is eventually replaced by Type I collagen with high tensile strength. The mechanical properties of scar tissue are determined by prolonged inflammation, which leads to dense and persistent weak Type III collagen [11]. The effect of suture techniques and suture materials on collagen synthesis and wound healing have been investigated in several experimental studies and both suture materials and suture techniques have been proven effective on Types I and III collagen production [12, 13].

The aim of this study was to investigate the total collagen amounts and the rate of Type I and Type III collagen synthesis in wound healing after midline and transverse incisions and reveal whether there was a difference between these two laparotomy techniques.

Materials and methods

This study was conducted at Necmettin Erbakan University KONUDAM Experimental Medicine Application and Research Centre. Animal Experiments Ethics Committee approval was obtained before the study. Institutional and national guidelines on the care and use of laboratory animals were followed and animal rights were protected in line with the principles of "Guide for the Care and Use of Laboratory Animals" [14]. All procedures were performed at Necmettin Erbakan University KONUDAM Experimental Medicine Application and Research Centre. A total of 24 BALB/c mice weighing 25 to 30 g were included in the study. General anesthesia was induced intraperitoneally with 2% xylocaine and 10% ketamine before the procedure. All mice were housed in groups of four in each cage under standard laboratory conditions. They were maintained at a constant room temperature of 20–21°C under a 12-hour light/dark cycle. The mice were given food and water ad libitum. The general condition and wounds of the mice were checked daily. No antibiotics were administered during the procedure. They were sacrificed by cervical dislocation after 28 days.

Surgical technique

The mice were randomly divided into three groups, each containing eight. The abdominal areas of the mice were shaved. The surgical area was sterilized with povidone-iodine. The suture length to wound length (SLWL) ratio of all suture materials was kept at 4:1 for the tensile strength of wounds to be equal in all mice [15]. All operations were performed by the same surgeon. The weight, general condition, and wounds of all mice were checked daily for 28 days.

No procedure was performed in the first group (control group, n=8) after anesthesia induction. The second group (midline group, n=8) underwent laparotomy along the linea alba with a 3 cm midline incision from the xiphoid (Figure 1). Peritoneum and linea alba were closed with 4*0 polypropylene nonabsorbable running suture (Prolene®, Ethicon GmbH& Co. KG, Norderstedt, Germany) and the skin was closed with 4/0 silk nonabsorbable interrupted sutures (silk® Doğsan Ltd. Co., Rize, Turkey). In the third group (transverse group, n=8), the laparotomy was performed with a 3-cm transverse incision at the umbilicus level. The peritoneum and musculoaponeurotic layer were closed with 4*0 polypropylene nonabsorbable running suture (Prolene®, Ethicon GmbH& Co. KG, Norderstedt, Germany) and the skin was closed with 4/0 silk nonabsorbable interrupted sutures (silk® Doğsan Ltd. Co., Rize, Turkey) (Figure 1).

Histochemical examination

All mice were sacrificed by cervical dislocation after 28 days. Then, the skin was removed, and an abdominal wall tissue of about 8 cm^2 (4x2cm) was totally excised with laparotomy lines remaining inside the incision. In the control group, an abdominal wall tissue of 8 cm^2, including the midline and transverse lines, was excised from the periphery of the umbilicus. The samples were fixed in 10% formaldehyde solution. A single well experienced pathologist who was blinded to the study design evaluated each specimen. Five-six mm thick sections obtained from two different layers of the wound were stained with hematoxylin/eosin, Masson Trichrome, and reticulin histochemical stains and then, evaluated under a light microscope (Figure 2).

Collagen fibers stained blue with the Masson Trichrome staining were evaluated as the sum of Type I and Type III collagen fibers (total collagen) (Figure 2). The density of these fibers was scored from one to five according to the following data [16].

Collagen (+): Collagen in the form of a single fiber.

Collagen (++): Collagen in the form of multiple fibers.

Collagen (+++): Collagen is more dense but loose.

Collagen (++++): Collagen covers the microscopic area but there are gaps between them.

Collagen (+++++): Collagen covers the microscopic area and has a very dense structure.

Figure 1: Images taken immediately after laparotomy and images taken on the 28th postoperative day A: 3-cm incision line identified at the level of the umbilicus before the transverse incision, B: Continuous closure of the fascia after transverse laparotomy, C: Healing in the midline incision line in the tissue sample taken 28 days after midline laparotomy D: 3-cm incision line identified at the midline before the midline incision E: Skin closed with single sutures after midline laparotomy, F: Healing in the transverse incision line in the tissue sample taken 28 days after transverse laparotomy.

Figure 2: Histochemical examination images of the subjects 1A: Tortuous collagen bundles stained in pink color after hematoxylin-eosin staining in the dermis and fascia in the control group (x40), 1B: Tortuous total collagen density stained in blue color after MASSON-TRICHROME staining in the dermis and fascia in the control group (x40), 1C: Type I collagen fibers stained in color ranging from yellow to dark yellow after reticulin staining at a greater amount in the dermis and fascia in the control group (x40) 2A: Granulation tissue area, inflammatory cells, foreign body (suture material), giant cells, and collagen after hematoxylin-eosin staining in the transverse group (x100), 2B: Loose collagen fibers and granulation tissue area stained in blue color after MASSON-TRICHROME staining in the transverse group (x100), 2C: Type I (dark yellow) and type III collagen fibers (fine black fibers) together after reticulin staining in the transverse group (x100). 3A: Less collagen density and granulation tissue area in the dermis and fascia after hematoxylin-eosin staining in the midline group (x40), 3B: Tighter collagens (blue color) with spaces in between after MASSON-TRICHROME staining in the midline group (x100), 3C: Granulation tissue area with denser and thicker type I collagen fibers (yellow colored) and rare fine type III collagen fibers (black colored) after reticulin staining in the midline group (x100)
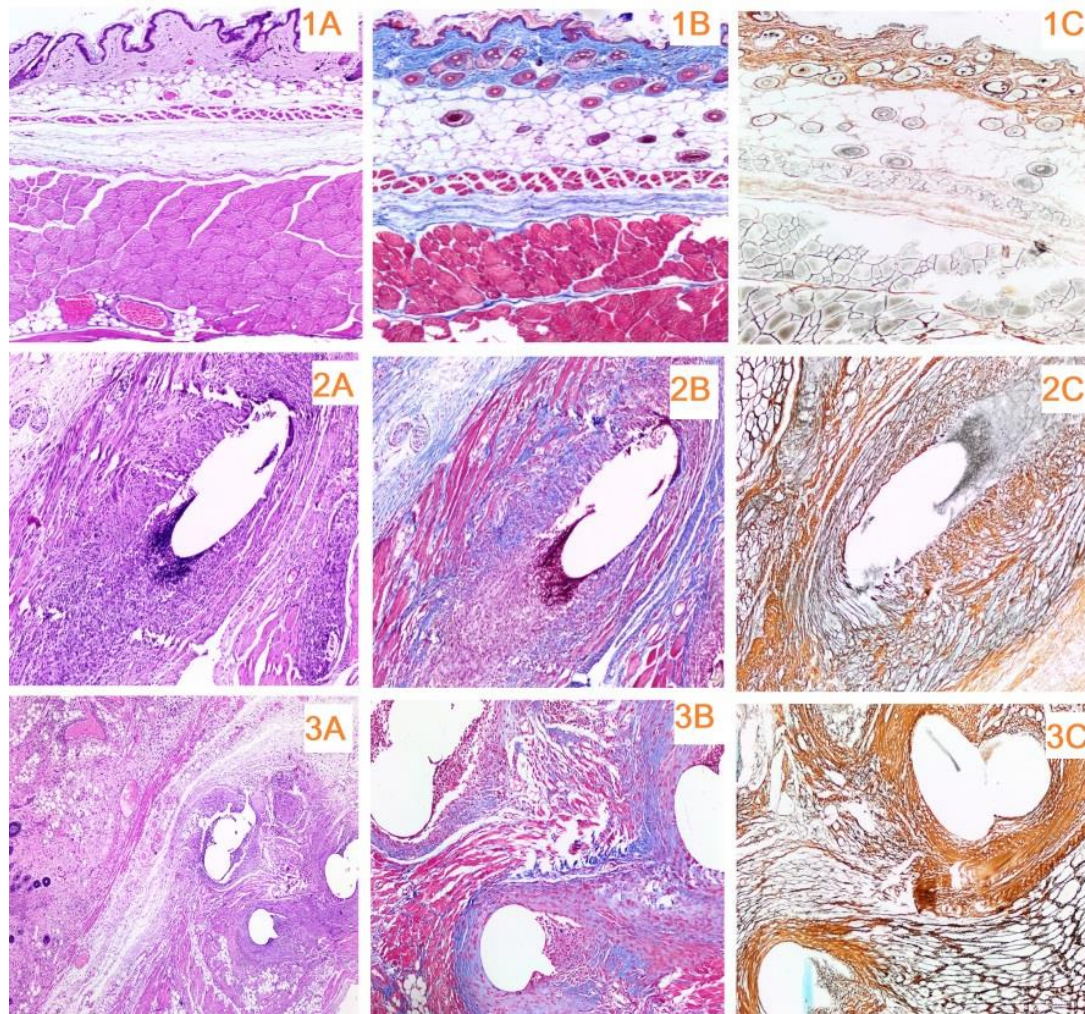
The fibers observed in the form of thin black lines with the reticulin histochemical staining indicated Type III collagen fibers. Other thicker lines, stained from yellow to dark yellow showed Type I collagen fibers (Figure 2). Measurements were semi-quantitative, and the rate of Type I and III collagens were recorded in percentage (%). Collagen I/Collagen III ratio was used to calculate maturation index [17].

Statistical analysis

Data were expressed as mean, standard deviation, minimum and maximum. Kolmogorov–Smirnov test was used to determine whether data were normally distributed. Since they were not, Tamhane's T2 post hoc test with ANOVA was used for group comparisons. Statistical analysis was performed using SPSS version 21.0 software (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, United States). A P-value <0.05 was considered statistically significant.

Results

Total collagen density

There was a slight increase in total collagen density in laparotomy groups (midline and transverse) compared to the control group, and the mean total collagen density in the transverse group was insignificantly higher than the other groups ($P=0.248$ and $P=0.486$ for the control and midline groups, respectively) (Table 1). Four positive total collagen density values were observed in three samples in the transverse group whereas a maximum of three positive total collagen density values were observed in other groups.

Table 1: Distribution and comparison of collagen density and collagen subtypes by groups

| Collagen Data	Control Group Mean (SD) (Min-Max)	Midline Group Mean (SD) (Min-Max)	Transverse Group Mean (SD) (Min-Max)	P-value
Total Collagen density	2.12 (0.834) (1-3)	2.37 (0.744) (1-3)	3.00 (1069) (1-4)	0.901[a] 0.248[b] 0.486[c]
Type I Collagen rate (%)	98.12 (2.587) (95-100)	65.62 (20.604) (30-85)	76.87 (14.37) (60-90)	0.008[a] 0.012[b] 0.541[c]
Type III Collagen rate (%)	1.87 (2.587) (0-5)	34.37 (20.604) (15-70)	23.12 (14.376) (10-40)	0.008[a] 0.012[b] 0.541[c]
Type I/Type III collagen rate	69.62 (41.921) (19-100)	2.82 (1.875) (0.43-5.67)	5.145 (3.505) (1.5-9)	0.001[a] 0.001[b] 0.336[c]

[a]: control group vs. midline group, [b]: control group vs. transverse group, [c]: midline group vs transverse group

Type I and Type III

The rate of Type I collagen, which was an indicator of mature collagen, was higher in the control group than in both the midline and transverse groups ($P=0.08$ and $P=0.01$, respectively) (Table 1). In the control group, the Type I collagen rate was 100% in half of the samples and 95% in the other half. Midline group had the lowest Type I collagen rate. Type I collagen was identified at a rate of 30% in one sample in the midline group, whereas at least one sample had 60% Type I collagen in the transverse group. Type I collagen rate was slightly higher in the transverse group than in the midline group (Table 1, Figure 3).

The rate of Type III collagen, which was an indicator of immature collagen, was lower in the control group than the other groups ($P=0.008$ and $P=0.012$ in the midline and transverse groups, respectively) (Table 1, Figure 3). Type III collagen rate was insignificantly lower in the transverse group than in the midline group ($P=0.541$) (Table 1, Figure 3).

Figure 3: Levels of type I and type III collagen concentrations and maturation index in groups
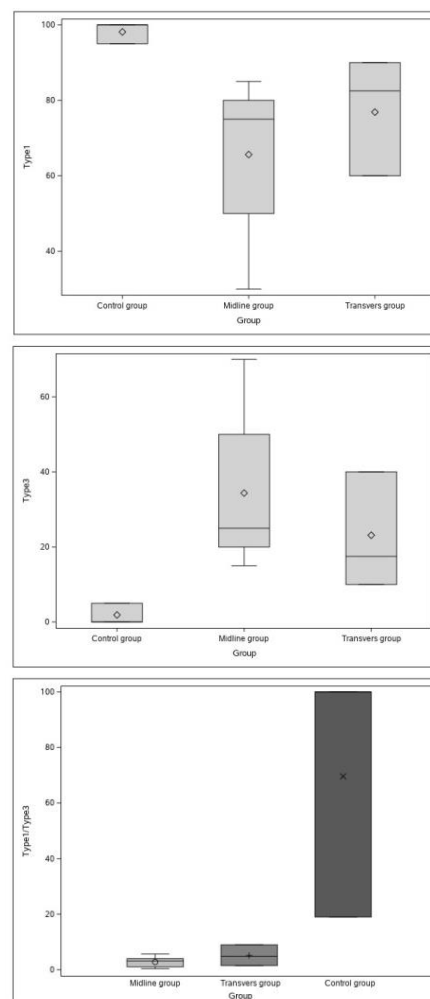
Maturation index

The maturation index was significantly higher in the control group compared to the laparotomy groups ($P=0.01$). The maturation index was higher in the transverse group than the midline group, but the difference was not statistically significant ($P=0.336$) (Table 1, Figure 3).

Discussion

In this experimental animal study, we compared collagen changes during wound healing after transverse and midline laparotomy incisions. Collagen is the most important component of mature connective tissue scar. During the tissue repair process, newly formed connective tissue containing capillaries and fibroblasts (granulation tissue) fills the gaps caused by dead cells and liquefaction of debris. The fibroblasts in this tissue produce collagen. Collagen is a family of structural proteins, the consistency, resilience, and durability of which vary depending on environmental influences and functional requirements. There are different types of collagen. Most of the collagen in the skin and tendons consists of Type I and Type III fibers. Therefore, other types of collagen can be excluded during the calculation of the total collagen amount in these areas.

Most of the studies conducted on laparotomy techniques so far have investigated suture techniques, suture materials, and wound tension [8, 16, 18, 19]. In an animal experiment, the bursting pressure of the two incisions after healing was analyzed and the pressure of the transverse incision was proven more durable [20]. However, the relationship with collagen is not

mentioned in this study. Although laparotomy closure techniques are known to influence the transverse tensile strength of healing after laparotomy surgeries and the incidence of incisional hernia formation, it has not been evaluated whether this effect is mediated by a direct influence of transverse and midline laparotomies on the collagen content and the collagen subtypes of the regenerating tissue. Therefore, this is the first study comparing the collagen amounts in wounds healed after midline and transverse laparotomy techniques.

The advantages of transverse and midline laparotomies are still controversial [8, 21]. Many studies have reported that the incidences of pulmonary and wound complications and incisional hernia are lower in the transverse laparotomy technique compared to the midline technique [4, 10, 22]. In these studies, the main reason for superiority has been attributed to the fact that the incision is parallel to the anatomical structures (muscle, vascular, nerve, etc.) in transverse incisions and it therefore causes less anatomical damage, ensuring that local wound healing is not adversely affected, and that minimal wound tension occurs since the incision is perpendicular to the major abdominal wall [23]. Short-term failures are often attributed to technical reasons, however, the most important factor determining wound durability in the long term is the density and type of collagen synthesis in the incisional region [19]. In the present study, it was aimed to investigate the differences between these two techniques in terms of collagen synthesis in wound durability rather than the technical and anatomical advantages of the transverse incision compared to midline incisions.

Parkinson et al. have reported that the density of the collagen determines the tensile strength of the structure [24]. Nevertheless, the rise in mean collagen fibril diameters in regenerating tissue occurs when the thin fibers of initially formed Type III collagen are replaced by the mature fibrils of Type I collagen, which, in conjunction with other collagen types, leads to definite tissue architecture and mechanical stability [25, 26]. In the present experimental study, total collagen density, which affects wound durability, Type I collagen synthesis, and maturation index were relatively high in the transverse incision technique whereas Type III collagen synthesis was relatively lower.

In a study by Höer et al., different suture techniques and materials used in laparotomy closures and SLWL ratio have been reported to affect both collagen synthesis and wound healing outcomes [19]. In the same study, a higher amount of collagen synthesis has been observed in wounds closed with an SLWL ratio of <4:1 and running sutures [19]. Therefore, all laparotomy wounds were closed with an SLWL of 4:1 using monofilament non-absorbable continuous sutures to ensure that our study was under optimal conditions.

Hydroxyproline analysis is considered the gold standard in measuring the amount of collagen in biological tissues [27]. However, hydroxyproline analysis has some limitations in terms of sensitivity, specificity, and accuracy, as well as difficulties of clinical approach [28, 29]. In an article, it has been reported that determining the amount and types of collagen by histopathological analysis is as effective as the hydroxyproline level [26]. Therefore, histochemical methods were used to determine collagen density and collagen types in the present study.

We believe that the present study will shed light on future clinical studies as a parameter to show the differences between these two incisions in terms of durability. We are aware that the disputable translation of results from animal experiments to human conditions can raise serious questions due to the different mechanical influences on the incision and genetic polymorphism influencing wound repair.

Conclusion

Although relative differences were observed in total collagen density, there were no significant differences between midline and transverse laparotomies. Type I and Type III collagen rates, total collagen density and maturation index were similar between both techniques.

Acknowledgments

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Journal of Surgery and Medicine

Review of 30 pulmonary hamartoma cases: Follow-up and treatment

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Abstract

Background/Aim: The most common benign tumor of the lung is hamartoma. Lung hamartomas are tumors of benign mesenchymal origin with intraparenchymal or endobronchial localization. They are more common in the 40-60-years age range and among males. It is important to distinguish hamartomas from malignancies due to their radiological appearance. The main treatment is surgical excision. They tend to grow slowly, and malignant transformation is rare. Therefore, the decision of resection or follow-up and timing of the surgical intervention are important. In our study, we aimed to present our follow-up and treatment results and recommendations of 19 years of pulmonary hamartoma experiences.

Methods: In this case series, the data of 30 patients with hamartomas as diagnosed by histopathological examination, who underwent surgical resection, bronchoscopy, and transthoracic lung biopsy between January 2001 and May 2020 were analyzed retrospectively. Radiologic and nuclear medicine imaging features, which are clinically important, were divided into groups and compared.

Results: The mass was removed in 12 (40%) patients by enucleation, in 5 (16.7%) patients, by wedge resection, in 3 (10%) patients, by bronchoscopy, and in 1 (3.3%) patient, by bronchotomy, segmentectomy and lobectomy. Seven (23.3%) patients were diagnosed with tru-cut biopsy and did not undergo total mass excision. Trans-thoracic fine needle biopsy (TTFNB) was performed in 7 (23.3%) patients and histopathological diagnosis could not be obtained in any of these biopsies. Concomitant with hamartomas, lung squamous cell carcinoma, lung malignancy in the contralateral lung, prostate carcinoma, and leiomyoma were found in one patient (3.3%) each.

Conclusion: Because of their slow growth and rare malignant transformation, lung hamartomas should be diagnosed with less invasive methods. The patients should be followed carefully unless they are symptomatic.

Keywords: Hamartoma, Pulmonary hamartoma, Pulmonary nodule

Introduction

The most common benign tumor of the lung is hamartoma [1, 2]. Lung hamartomas are tumors of benign mesenchymal origin with intraparenchymal or endobronchial localization [1]. They contain different components and are named according to the dominant tissue [2]. Although some genetic factors are suspected etiologically, no definite risk factors have been identified [3, 4]. The incidence of lung hamartoma is 0.025% –0.32% [1, 5]. They are more common in the 40-60-year age range and among males [2]. Their diameter is usually less than 2-3 cm [1], so they are often asymptomatic and detected incidentally [1, 2]. The main treatment is surgical excision [5]. They tend to grow slowly, and rarely undergo malign transformation. Therefore, the decision of resection or follow-up and timing of the surgical intervention are important.

In our study, we aimed to present our follow-up and treatment results and recommendations by sharing our 19-year experience with pulmonary hamartomas.

Materials and methods

Patient selection criteria and general features

The data of 31 patients with histopathological diagnoses of hamartoma who underwent surgical resection, bronchoscopy, transthoracic lung biopsy at Kocaeli University Hospital Department of Thoracic Surgery between January 2001 and May 2020 were reviewed retrospectively. The data used in our study were accessed through hospital files, hospital radiological imaging systems, and central records (e-Nabız, Mernis etc.). One patient with a diagnosis of hamartoma outside the lung parenchyma was excluded from the study. Finally, 30 hamartoma patients with sufficient data were included. Age, gender, smoking, illness histories, symptoms, tumor size-localization, radiological features, surgical technique, transthoracic biopsies, and accompanying malignancies were analyzed. Radiologic and nuclear medicine imaging features (calcification, fat density, diameter size, FDG uptake) were noted.

Approval 2020/262 was received from Kocaeli University Faculty of Medicine Ethics Committee on 11/09/2020.

Surgical features

All admitted patients underwent Thoracic Tomography (CT). Blood tests (hemogram, coagulometry, biochemistry), pulmonary function test (PFT), and echocardiography (EKO) were performed. The size of the tumor was determined by pathological examination in resected tumors and from the thorax CT images in non-resected ones. Those localized in one third of the medial hemithorax or associated with the mediastinal pleura were considered central tumors, while others were noted as peripheral.

Bronchoscopic or transthoracic biopsy were performed preoperatively in some patients to obtain a diagnosis. Patients diagnosed before the operation were not operated. Punch biopsy was performed in endobronchial lesions in bronchoscopic biopsy, while fine needle and tru-cut biopsies were performed in transthoracically.

Operations by posterolateral thoracotomy were performed to provide histopathological diagnosis and treatment. The operation type depended on the experience of the surgeon performing the operation. Radiological appearance features, lack of uptake on Positron emission tomography (PET-CT), and frozen pathological examination were effective in this decision. Enucleation was performed in lesions where the entire mass could be delivered, wedge resection was done in other patients, and lobectomy was performed in 1 patient due to concomitant primary lung malignancy. In enucleation, the tissue was repaired with direct sutures, while linear tissue staples were used in wedge resections. One drainage tube was inserted in all operations.

Postoperatively, patients were followed up by chest radiography and tube thoracostomy. Tubes that had no air leakage for more than 24 hours and whose daily drainages were less than 100 cc were withdrawn.

Follow-up

Routinely, a physical examination was performed, and chest x-rays were obtained at the 1st and 3rd weeks after discharge. Patients who were properly followed-up by us or whose health records could be found in the central recording system (e-Nabız) were included in the study.

Statistical analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk's tests were used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean (standard deviation) or (in case of no normal distribution) median (25th-75th percentile). Categorical variables were summarized as numbers (percentages).

Results

The mean age of the patients was 58.63 (12.08) years. Twelve (40%) patients were in the 40-60 age range and 18 (60%) were in the other age groups. Twenty-two (73.3%) patients were male and 8 (26.7%) were female. The median follow-up time was 5.76 (1.92-9.58) years. General demographic features are presented in Table 1 and hamartoma features are presented in Table 2.

Table 1: General characteristic

	Total (n=30)
Age (mean (SD)) (year)	58.63 (12.08)
Sex (n,%)	
Male	22 (73.3%)
Female	8 (26.7%)
Smoking History (n,%)	84(84.8%)
Disease History (n,%)	
Absent	16 (53.3%)
Pulmonary	1(3.3%)
Cardiovascular	5 (16.7%)
Other	8 (26.7%)
Symptom (n,%)	
Asymptomatic	20 (66.7%)
Cough	2 (6.7%)
Chest pain	8 (26.7%)

n: number, SD: Standard Deviation

Among the patients included in our study, transthoracic fine needle and tru-cut biopsies were performed in 7 (23.3%) patients each. Histopathological diagnosis was obtained in all patients who underwent tru-cut biopsy and none who underwent fine needle biopsies. Of these tumors diagnosed with tru-cut biopsies, 3 (42.9%) had calcification, 3 (42.9%) had fat density, and 4 (57.1%) had a diameter of 3 cm or more. The mean tumor size was 2.54 (0.85) cm. PET-CT was performed in 6 out of these 7 patients and 4 (66.67%) had no F-18 fluoro-2-deoxy-glucose

(FDG) uptake, 1 (16.67%) had no significant FDG uptake, while 1 (16.67%) showed significant FDG uptake.

Table 2: Tumor features

	Total n=30	
Localization n (%)		
Right upper lobe	4 (13.3%)	53.3%
Right middle lobe	3 (10%)	
Right lower lobe	9 (30%)	
Left upper lobe	8 (26.7%)	46.7%
Left lower lobe	6 (20%)	
Central / Peripheral n (%)		
Central	4 (13.3%)	
Peripheral	26 (86.7%)	
Tissue (n,%)		
Lung Parenchyma	26 (86.7%)	
Bronchial	4 (13.3%)	
Radiological Features n (%)		
Calcification	11 (36.7%)	
Fat Density	13 (43.3%)	
Tumor size n (%)		
<3 cm	6 (20%)	
≥3cm	24 (80%)	
Mean (SD) (cm)	1.98 (0.86)	
PET-CT n (%)		
Absent	15 (50%)	
No up-take	10 (66,7%)	
SUV-max < 2.5	2 (13.4%)	
SUV-max > 2.5	3 (20%)	

PET-CT: Positron Emission Tomography, SUV-max: Maximum standardized uptake value

The mass was removed in 12 (40%) patients by enucleation, in 5 (16.7%) patients, by wedge resection, in 3 (10%) patients, by bronchoscopy, and in 1 (3.3%) patient, by bronchotomy, segmentectomy and lobectomy. Total mass excision was not performed in seven patients diagnosed with tru-cut biopsies. Frozen pathological examination was performed in 14 (60.87%) cases during the operations.

Concomitant with hamartomas, lung squamous cell carcinoma, lung malignancy in the contralateral lung, prostate carcinoma, and leiomyoma were found in one patient (3.3%) each.

Discussion

Hamartomas constitute 3% of all lung tumors [6] and 6% of solitary pulmonary nodules [4, 5]. It is common in the male gender and between the 40-60-year age range [5, 6]. In our study, 73.3% of the patients were male, 40% were between 40-60 years of age.

Most hamartomas originate from the parenchyma and are localized peripherally [2,5]. In the study of Haberal et al. [2] including 24 patients, all lesions were of parenchymal origin, more frequently in the right lung, and 71% were peripherally located. In another study, 85% peripheral location was reported [6]. Endobronchial hamartomas are reported in 3-19.5% [5]. In our study, hamartomas were often localized in the lung parenchyma and peripherally. It was bronchial in 13.3%, found more frequently (53.3%) in the right lung and most frequently in the lower lobe of the right lung.

Hamartomas are often asymptomatic [2, 5-7]. Symptomatic ones are usually those that are large enough compress the endobronchial or surrounding bronchial-vascular structures. The most common symptoms are hemoptysis, cough, shortness of breath, and chest pain [1]. In our study, patients were often asymptomatic, and the most common symptom was chest pain.

Their growth rate is slow [8]. Most are small, and only a few giant hamartomas have been reported [1]. Lesion sizes are usually less than 2-3 cm [1, 2]. In the study of Haberal et al. [2], the size of 54.2% were 3 cm and less. The mean lesion size was 2.3 cm in the study of Çaylak et al. [6]. In our study, the mean lesion size was 1.98 cm and 80% was less than 3 cm in diameter.

Chest radiography and thoracic tomography (CT) can be used to aid diagnosis, but definitive diagnosis is obtained by histopathological examination [1]. Parenchymal hamartomas are usually well-circumscribed nodules with calcification on chest radiography. Endobronchial ones may yield indirect signs such as increased aeration or atelectasis in a hemithorax. Calcification (especially popcorn) in the mass, high fat content (up to 50%), slow growth, peripheral localization and lack of invasion are findings suggestive of hamartoma on thorax CT images [1, 2, 5]. About 10-30% contain calcification, and 50% contain fat, which is pathognomonic [4, 6]. In our study, we found 36.7% calcification and 43.3% fat content, close to the rates in the literature. In endobronchial hamartomas, no significant activity is expected in PET-CT except for some hamartomas with low lipid ratio [2]. Due to the interval in which our study was conducted, PET-CT was not studied in some patients, and in those who underwent PET-CT, 66.7% did not have any FDG uptake, while 20% of the patients had SUV-Max over 2.5.

It has been reported that needle aspiration biopsy is often insufficient for diagnosis [2, 5, 6]. In their study involving 20 patients, Çaylak et al. [6], 2 patients underwent TTFNB but could not be diagnosed histopathologically. In another study, transbronchial or transthoracic needle aspiration was performed in 12 patients and 3 patients (25%) could be diagnosed [4]. Contrary to expectations, some studies reported 85% sensitivity [9] or 86% diagnosis rate [10] in needle biopsy. Hamper et al. [10] stated that the diagnostic thoracotomy rate would decrease significantly with needle biopsy. Some studies state the necessity of surgery for definitive diagnosis [2]. While TTFNB was performed in 7 patients in our study and histopathological diagnosis was not obtained, diagnosis was obtained with tru-cut biopsy in 7 patients. Considering the distribution of tumor characteristics of patients diagnosed with tru-cut biopsy, no statistically significant difference was found in PET-CT in terms of FDG up-take, or in Thoracic CT in terms of calcification or fat content of the mass. The number of patients with tumors larger than 3 cm was significantly higher among those who underwent tru-cut biopsy.

Bronchial carcinoma development is more common (7%) in patients with pulmonary hamartoma [6]. In two hamartoma studies with 24 and 39 patients conducted in our country, bronchogenic carcinoma association was reported in 2 patients each [11]. In one study, the risk of pulmonary malignancy in patients with hamartoma was 6.3 times higher than the general population [12]. In our study, there was 1 (3.3%) lung squamous cell carcinoma, 1 (3.3%) lung malignancy in the contralateral lung (6.6% in total), 1 (3.3%) prostate carcinoma, and 1 (3.3%) leiomyoma in patients simultaneously with hamartomas.

Surgical excision is sufficient in treatment [1]. Care should be taken to lose as little parenchyma as possible. Generally, enucleation or wedge resection is sufficient [5, 6]. Sometimes, large parenchymal resection or even pneumonectomy can be performed due to the hamartoma's location and its relationship with the surrounding tissue and symptoms [1]. Lobectomy rates between 6.7-26.3% and pneumonectomy rates between 1.5-13.3% have been reported [4]. Post-surgical mortality and morbidity is very low [2]. Forty percent of our patients underwent enucleation,

16.7% underwent wedge resection, 3.3% underwent lobectomy, and no pneumonectomy was performed. The indication for lobectomy was malignancy accompanying the hamartoma. No mortality or serious morbidity was observed in any of our patients.

Malignant transformation or recurrence has been reported very rarely [5]. In two studies which 15 and 20 patients underwent surgical treatment, recurrence [4, 6] or malignant transformation were not reported [6]. In a study that reported surgical resection in 39 patients, recurrence was reported in 1 (2.6%) patient, but no malignant transformation [5]. In another study on 52 patients, malignancy developed in the hamartoma excision site in 4 (7.69%) patients [12]. No recurrence or malignant transformation was observed in our follow-ups.

Since malignancy or recurrence may develop, who to follow and until when is another matter of discussion [5]. Some authors recommend surgery in young and middle-aged cases with a growing lesion or persistent symptoms [4, 5]. Guo et al. [5] reported that because hamartomas tend to grow and may cause malignancy by inducing chronic inflammatory processes, lesions larger than 2.5 cm, and solitary lesions which cannot be distinguished from malignancy, should be excised. In a study, resection was recommended for large lesions, those increasing rapidly in size, and symptomatic patients [7]. In another study, resection was recommended in young or middle-aged and symptomatic patients [9]. Some authors recommend follow-up in asymptomatic lesions proven by biopsy [7]. In our study, surgery was not performed in any of our patients due to their symptoms. In general, the procedure was performed for malignancy exclusion regardless of the size of the lesion (except size increase). We followed up 10 (33.33%) patients by diagnosing them with tru-cut biopsy or bronchoscopy.

The limitations of our study include low number of cases, although it was sufficient considering its incidence, and its retrospective nature. The study will expand with more case series in the future.

Conclusion

It is important to distinguish hamartomas from malignancy due to their radiological appearance. Because of their slow growth and low risk of malignancy, hamartomas may be followed closely until they become symptomatic. Their definitive treatment is surgical resection.

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Factors affecting CPAP compliance in patients with obstructive sleep apnea

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Abstract

Background/Aim: Continuous positive airway pressure (CPAP) is the most effective treatment for obstructive sleep apnea (OSA), but adequate patient compliance is required for treatment to achieve clinical success. This study aimed to determine factors affecting compliance with CPAP therapy in patients with OSA.

Methods: In this retrospective cohort study, the records of patients that started CPAP treatment due to OSA between January 1, 2018 and August 30, 2020 were reviewed. The patients were divided into two groups based on their CPAP compliance: Group 1 included those who used CPAP regularly, and Group 2 included irregular users. Parameters such as age, gender, body mass index, apnea-hypopnea index, and educational status were compared between the groups.

Results: Baseline apnea-hypopnea index (AHI) and oxygen desaturation index (ODI) of patients using CPAP regularly were higher than irregular users ($P=0.003$, $P=0.045$, respectively). There was no significant difference between the groups in terms of age, gender, and body mass index ($P=0.542$, $P=0.120$ and $P=0.796$, respectively). In multivariate logistic regression analysis, low AHI, low ODI and low educational level were independent risk factors affecting CPAP compliance ($P=0.010$, $P=0.016$ and $P=0.047$, respectively).

Conclusion: According to the results of this study, low AHI and ODI levels and low education status were risk factors for non-compliance with CPAP treatment. Therefore, patients with these features may require closer follow-up for early identification of CPAP treatment failure due to non-compliance.

Keywords: Continuous positive airway pressure, Obstructive sleep apnea, Compliance, Apnea-hypopnea index

Introduction

Obstructive sleep apnea (OSA) is a common disease characterized by partial or complete obstruction of the upper airway during sleep. The prevalence of OSA has been gradually increasing, and various studies on adults have shown it to vary between 15-45% [1, 2]. It is known that OSA is associated with many systemic diseases such as hypertension, cardiovascular problems, cerebrovascular events, pulmonary hypertension, and depression [3]. In addition, by causing daytime sleepiness, OSA can lead to decreased work performance and traffic accidents [4].

Continuous positive airway pressure (CPAP) applied with a nasal mask during sleep is the most common treatment for OSA. The positive pressure provided by the CPAP machine allows the intraluminal pressure to exceed the pressure created by the surrounding tissues. Thus, upper airway collapse does not occur, and obstructive apnea-hypopnea events are prevented. It has been shown that CPAP improves day and night symptoms of OSA, normalizes sleep structure, reduces cardiovascular morbidity and mortality, improves cognitive functions, and increases quality of life [5-7].

Although CPAP is an extremely safe and effective method of treatment, its effectiveness is closely related to the rate of adherence to it [8]. The prevalence of CPAP non-compliance (using the CPAP machine for less than 4 hours per night), which is an important challenge in the management of OSA patients, ranges from 29-83% [9].

There are many studies in the literature examining the factors affecting CPAP compliance in OSA patients. The aim of this study was to examine the relationship between CPAP compliance and factors such as age, gender, apnea-hypopnea index (AHI), body mass index (BMI), oxygen desaturation index (ODI), and educational status.

Materials and methods

Records of patients who started CPAP treatment due to OSA in a sleep laboratory of a tertiary hospital between January 1, 2018 and August 30, 2020 were retrospectively reviewed. The study was approved by Yozgat Bozok University Clinical Research Ethics Committee (2017-KAEK-189_2021.02.10_21) and the Helsinki Declaration rules were followed throughout the study.

All patients were clinically evaluated in the sleep medicine department before and after polysomnography. Demographic data of the patients including age, gender, education level, and BMI were recorded. Polysomnographies were performed using a 31-channel ALICE 6 LDe (Respironics, PA, USA) device. The average number of apnea and hypopnea per hour (AHI) and the average number of episodes per hour with desaturation of >4% (ODI) were obtained from the PSG reports. Patients who were recommended to use CPAP had at least one overnight trial of CPAP using the auto-titration technique. Technicians in the sleep clinic trained patients on the basics of using CPAP.

Patients that were older than 18 years old, diagnosed with OSA, given a CPAP device, and accepted to fill out a questionnaire on CPAP compliance were included in the study.

Patients were called for follow-up and information about compliance was obtained.

The patients included in the study were divided into two groups. Regular CPAP users (using CPAP for at least 4 hours a night) were included in Group 1, while those who did not use it regularly were included in Group 2. Both groups were compared in terms of age, gender, BMI, AHI, and ODI values. The independent values of these factors in predicting CPAP compliance were also investigated.

Statistical analysis

SPSS software (version 20.0 for Windows, IBM Corp., Armonk, NY, USA) was used for all data analyses. Descriptive data were given as mean (SD). Kolmogorov-Smirnov/ Shapiro-Wilk's tests were used to determine whether continuous variables were normally distributed. Mann-Whitney U test and Student t-test were used for numerical data with and without normal distribution, respectively. A logistic regression analysis was performed to determine independent predictors of CPAP compliance. The receiver operating characteristic (ROC) test was applied to determine the cutoff value of the data in affecting CPAP compliance. A P-value of <0.05 was considered statistically significant.

Results

There was no significant difference between the groups in terms of age, gender, and BMI. The mean AHI, ODI values and education level of Group 1 were significantly higher than those of Group 2. The demographic data, BMI, AHI, ODI and education levels of the groups are shown in Table 1. In multivariate logistic regression analyses, low AHI, low educational level and low ODI were independent risk factors affecting CPAP compliance. There was no significant association between CPAP compliance and BMI. The correlation between CPAP compliance and age, gender, AHI, ODI, BMI, and educational level are shown in Table 2.

Table 1: Comparison of demographic and clinical parameters in patient groups

Parameters	CPAP non-compliers (n=30)	CPAP compliers (n=30)	P-value
Gender (F/M)	11 F / 19 M	14 F / 16 M	0.120
Age in years	53.27(10.14)	54.90 (10.47)	0.542
BMI, kg/m2	29.58 (2.94)	29.83 (3.48)	0.796
AHİ	31.78 (14.94)	55.69(32.53)	0.003
ODİ	36.64 (14.91)	49.23 (31.96)	0.045
Education level	8.40 (3.38)	10.50 (3.87)	0.031

Data presented as mean (SD). CPAP: continuous positive airway pressure, F: female, M: male, BMI: body mass index, AHI: Apnea-hypopnea index, ODI: oxygen desaturation index, SD: standard deviation

Table 2: Multivariate logistic regression model of potential factors affecting CPAP compliance

	B	P-value	OR	95% C.I. Lower	Upper
Age	-0.009	0.881	0.991	0.884	1.111
Gender	1.292	0.218	3.641	0.465	28.478
AHI	0.527	0.010	1.693	1.136	2.523
BMI	-0.242	0.205	0.785	0.539	1.142
ODI	-0.479	0.016	0.619	0.419	0.916
Education level	0.337	0.047	1.401	1.004	1.953

CPAP: continuous positive airway pressure, BMI: body mass index, AHI: Apnea-hypopnea index, ODI: oxygen desaturation index, SD: standard deviation OR: odds ratio, CI: confidence interval.

In patients with a definitive diagnosis of CPAP incompliance, statistically significant parameters (AHI, ODI, and education levels) were evaluated in ROC curve analysis, and sensitivity and specificity of each parameter were calculated. According to the ROC analysis, AUC values of AHI, ODI, and education levels were 0.724, 0.616 and, 0.655 respectively (Figure 1). The optimal AHI, ODI and educational level cutoff values for distinguishing the two groups were 27.2 (80% sensitivity and 65%

specificity), 29.7 (77% sensitivity and 50%), and 9.5 years (70% sensitivity and 60% specificity), respectively (Table 3).

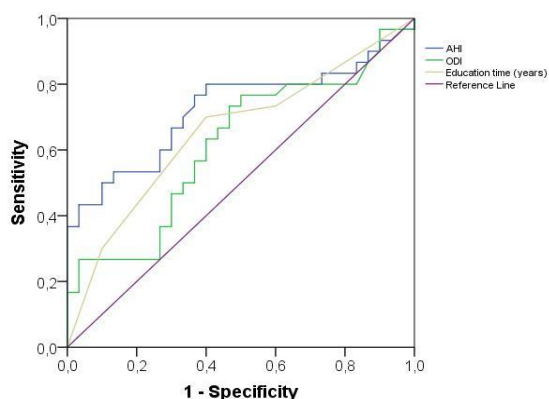Figure 1: ROC analysis for performance to predict CPAP compliance of AHI, ODI and education level

Table 3: ROC curve characteristics of the discriminative factors to detect CPAP compliance

	AUC	SD	P-value	95% Cl	Cutoff value	Sensitivity%	Specificity%
AHI	0.724	0.068	0.003	0.591-0.858	27.2	80	65
ODI	0.616	0.074	0.124	0.471-0.760	29.7	77	50
Education level	0.655	0.072	0.039	0.515-0.795	9.5	70	60

Values that are statistically significant are indicated in bold. ROC: receiver operating characteristic, AUC: area under curve, AHI: Apnea-hypopnea index, ODI: oxygen desaturation index.

Discussion

There are various options for the treatment of OSA, including behavioral methods such as weight loss, cessation of smoking and alcohol use, sleep position training, as well as other methods such as CPAP, intraoral appliance therapy and surgical intervention in the upper airway. However, the American Academy of Sleep Medicine recommends that CPAP be considered as both the first line and gold standard treatment for OSA [10].

CPAP is a very effective treatment for OSA; however, low patient compliance remains a significant problem. Although there is no globally accepted definition of good CPAP compliance, studies have shown that the patient should use CPAP for at least 4 hours a day to benefit from treatment. Therefore, to achieve an effective and successful CPAP treatment, it is necessary to identify factors affecting patient compliance and eliminate issues that have negative impact. These factors are diverse and can include disease and patient characteristics, treatment titration procedures, device factors, as well as psychological and social factors [11, 12]. The severity of OSA, daytime sleepiness, age, gender, and patient comorbidities can increase or decrease the use of CPAP [13].

Studies examining the relationship between OSA severity and CPAP compliance have revealed conflicting results. In some studies, no relationship was found between AHI and CPAP compliance [14, 15]. On the other hand, there are studies showing that CPAP compliance is better in severe OSA patients with high AHI [13, 16]. In our study, patients with good CPAP compliance had higher mean AHI values than patients with poor compliance. AHI value was an independent factor affecting CPAP compliance. In ROC analysis, AHI above 27.2 predicted CPAP compliance with 80% specificity and 65% sensitivity.

Kohler et al. [17] reported a positive correlation between CPAP compliance and high ODI value, which is another parameter that shows the severity of OSA. In another study,

Riachy et al. [18] showed that mean ODI was significantly higher in the CPAP-compliant patient group, and that higher ODI was an independent predictor for CPAP compliance. In the multivariate logistic regression analysis performed in our study, there was a strong positive relationship between high ODI value and CPAP compliance. Our results therefore confirm the findings of previous studies showing that OSA severity is a predictor of CPAP compliance.

In many studies, income level, region of residence, and years of education have been associated with CPAP compliance [19, 20]. This may be since people with high income can access services easier and individuals with higher education status are more aware of the risks of the disease. In our study, we also observed that higher education level was associated with better CPAP compliance.

Although there are conflicting results in the literature regarding the relationship between age, gender, BMI, and CPAP compliance, in large patient series, Kohler [17] and McArdle [21] stated that age, gender and BMI were not associated with CPAP compliance. In this study, we could not find a significant relationship between CPAP compliance and these factors. Therefore, we think that these factors should not affect decisions about CPAP treatment recommendations.

Limitations

Our study has some limitations. First, the CPAP usage times were self-reported, and not obtained from an objective data such as a compliance meter. The low number of patients is another limitation. In addition, the retrospective design of the study prevented us from obtaining data on the extent of the training of patients before beginning CPAP therapy. Future prospective studies, where the same investigator informs all participants to ensure that everyone is adequately and homogeneously informed, are needed to better understand the factors involved in CPAP compliance.

Conclusion

According to the results of this study, low AHI levels and low education status were risk factors for non-compliance with CPAP treatment. Therefore, patients with low AHI levels and low educational status may require closer follow-up for early identification of CPAP treatment failure due to non-compliance.

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The relationship of pre-operative laboratory parameters with endometrial cancer and prognostic factors

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Abstract

Background/Aim: Endometrial cancer, like many other malignancies, is associated with an inflammatory process, and complete blood count parameters have been studied as markers numerous times. Our study aimed to evaluate whether pre-operative complete blood count and biochemical parameters are related to some prognostic markers and stage of the disease in patients who underwent surgery for endometrial cancer.

Methods: One hundred seventy-five patients diagnosed with endometrial cancer operated in our clinic between January 2017 and December 2019 were evaluated in this retrospective cross-sectional study. We analyzed complete blood count parameters including hemoglobin, white blood cell count, platelet count, neutrophil count and percentage, lymphocyte count and percentage, mean corpuscular volume, mean platelet volume, red blood cell distribution width (RDW), neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and other biochemical parameters. Statistical methods were used to investigate their relationship with prognostic parameters such as tumor diameter, differentiation, and type, myometrial invasion, and FIGO stage. Long-term survival could not be examined because the long-term follow-up of patients was not available in the database.

Results: One hundred seventy-five patients were included in the study. The mean age of our patients was 61.3 (9.3) years. While the degree of myometrial invasion of the tumor was positively correlated with the patient's age, red cell distribution width, and NLR, it was negatively correlated with hemoglobin value, and lymphocytes percentage. We divided the patients into two groups as those with less and more than ½ thickness myometrial invasion. Age, red cell distribution width, NLR and PLR were higher in the group with more invasion ($P<0.05$ for all), and lower in type 1 endometrial cancer compared to type 2 ($P<0.05$ for all). MPV values were lower in grade 3 tumors compared to grades 1 and 2 ($P=0.022$), while neutrophil count was highest in patients with grade 3 tumors ($P=0.023$). According to our regression analysis, each 1-unit increase in the NLR predicted 1.06 times increased invasion of more than ½ of the myometrium ($P=0.05$).

Conclusion: The use of pre-operative complete blood count, liver, and kidney enzyme parameters may give an idea about the prognostic components, and stage of the disease in patients with a diagnosis or suspicion of endometrial cancer.

Keywords: Endometrial cancer, Complete blood count, Hemoglobin, Lymphocyte, Platelet

Introduction

Endometrial cancer is the most common gynecological cancer in high-income countries, and the second most common gynecological cancer worldwide after cervical cancer [1].

Risk factors for endometrial carcinoma are an excess of endogenous or exogenous estrogen without sufficient opposition from progestin. Other risk factors include tamoxifen therapy, increasing age, early menarche, obesity, nulliparity, diabetes mellitus, and hypertension, as well as genetic risk factors, such as Lynch syndrome [2].

Malignant tumors of the female genital tract are important causes of death worldwide [3]. Immune cells, and the inflammatory system plays multifaceted roles [4]. Virchow demonstrated the presence of leukocytes in neoplastic tissue. In 1876, he showed that cancer is affected by a systemic inflammatory response [5]. The response to inflammation involves some alterations. One of these changes associated with the hematopoietic system is related to leukocyte, and platelet levels [6]. Tumor tissue hosts leukocytes which have crucial inflammatory roles, and platelets are important sources of angiogenetic cytokines. Both are critically essential in tumor progression and overall survival through the triggering of inflammatory mechanisms [5].

Studies show that absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute lymphocyte count (ALC), NLR, monocyte-lymphocyte ratio (MLR), and PLR are significantly associated with different types of solid tumors like cervical, endometrial, and ovarian cancers [7, 8].

Complete blood count (CBC) is routinely performed during the pre-operative assessment of patients with cancer. ALC, AMC, NLR, PLR, Mean Platelet Volume (MPV), Mean Corpuscular Volume (MCV), Hemoglobin (Hb), Platelets (Plt), White Blood Cell (WBC), and RDW parameters reflect the inflammatory, and procoagulant states in cancer.

Increase in absolute neutrophil count and a decrease in absolute lymphocyte count results in NLR increase. Some studies found that NLR was associated with some types of cancer and progression of the disease [9–12].

PLR is defined as absolute platelet count divided by absolute lymphocyte count. Platelet count is a finding of systemic inflammation and can be used to distinguish cancer from benign pathologies. However the platelet-lymphocyte ratio (PLR) is an inflammatory marker and studied in malign tumors [13–16].

Platelets are studied in some studies on cancer. Thrombocytosis is reportedly associated with the development cancer and its progression [17, 18].

Fibrinogen is essential for coagulation cascade and inflammatory response. Plasma fibrinogen levels are correlated with systemic inflammatory diseases, tumors, and their progression. [19–22].

This study aimed to determine the best predictor of clinicopathological features between pre-operative CBC-derived inflammatory biomarkers and endometrial cancer.

Materials and methods

We conducted this retrospective cross-sectional study at Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital, Department of Obstetrics and Gynecology, Bursa, Turkey. The study groups consisted of patients who were treated for endometrial cancer between September 2016 and June 2019. This study was approved by Bursa Yüksek İhtisas Training and Research Hospital Ethics Committee with the number 2011-KAEK-25 2020/06-20.

Patients with incomplete pre-operative complete blood count data, a history of other cancers, splenectomy, chemotherapy and radiotherapy, steroid use, chronic systemic diseases, known myeloproliferative diseases and those with documented vitamin B12 or folate deficiencies were excluded from the study.

We analyzed one hundred and seventy-five patients diagnosed with endometrial cancer and evaluated hemoglobin values, white blood cell, thrombocyte, neutrophil, lymphocyte, mean erythrocyte volume, mean platelet volume, and erythrocyte distribution volume, which were examined within the last month before the operation. Also, the relationship between NLR, which is the division of neutrophil count to lymphocyte count, and PLR, which is the division of the platelet count to the lymphocyte count, with prognostic parameters such as tumor diameter, tumor differentiation, tumor type, myometrial invasion and FIGO stage were studied using statistical methods.

We classified endometrium cancer histomorphologically as Type-1 and Type-2 according to the Bokhman classification [23].

Statistical analysis

Windows-based SPSS 24.0 statistical analysis program (SPSS Inc., USA) was used for statistical analyses. Variables were examined visually (histograms, probability charts) and using analytical methods (Shapiro-Wilk test) to determine whether the data showed normal distribution. In descriptive analyses, variables were presented as mean (standard deviation), median (minimum-maximum (min-max)), U value, frequency (n), and percentage (%) at 95% confidence interval (95% CI). Student t-test and Mann-Whitney U tests compared normally and non-normally distributed variables, respectively, in the two-group analysis. ANOVA and Kruskal Wallis tests analyzed variables involving more than two groups. Pearson and Spearman's tests were performed to show the correlations between normally and non-normally distributed variables, respectively. First, univariate analyses were used to determine the degree of myometrial invasion of the endometrial tumor, tumor type, and variables predicting differentiation. Independent predictors were examined by including variables with $p < 0.25$ in univariate analyses into multivariate analyses, in which the ENTER method was used. The compatibility of the models with the data was evaluated with the Hosmer-Lemeshow test. A multivariate linear regression model was used to evaluate the effect of parameters on tumor size. Ordinal regression model evaluated the effects of the parameters on tumor stage according to FIGO classification. The cases where the type 1 error level was below 5% were considered statistically significant.

Results

The demographic and laboratory characteristics and descriptive analyses of the patients are presented in Table 1. The mean age of one hundred seventy-five patients included in the study was 61.3 (9.3) years.

Table 1: Descriptive analysis of data

Characteristics and Laboratory data	Endometrial cancer (n=175) Mean (SD) Median (min-max)
Age*	61.26 (9.3)
Duration of hospitalization (day)	7 (45-3)
Hemoglobin (g/dl)	12.6 (17.3-6.3)
Mean corpuscular volume (fl)	84.2 (58.6-97.5)
Mean platelet volume (fl)*	9.11 (1.2)
Red cell distribution width (%)	14.1 (30.7-11.6)
Neutrophil count (10^3/ml)	5.2 (23.9-1.6)
Lymphocyte count (10^3/ml)	2 (8-0.3)
Neutrophil percentage (%)*	66.8 (11.2)
Lymphocyte percentage (%)	25.9 (67.6-2.4)
White blood cell (mcl)*	9.800 (7.700)
Platelets (mcl)	287.000 (728.000-135.000)
Creatinine (mg/dl)	0.8 (9-0.3)
Alanine Transaminase (ALT) (u/l)	16 (114-1)
Aspartate Transaminase (AST) (u/l)	20 (375-4)
Plasma glucose level (mg/dl)	113 (286-67)
Fibrinogen	346 (712-167)
Neutrophil/Lymphocyte Ratio	2.5 (45.3-0.7)
Platelet/Lymphocyte Ratio	140 (703-36)
Tumor Diameter (cm)	4 (30-0.3)

g/dl: gram/deciliter, fl: femtolitre, ml: milliliter, mcl: microliter, %: percent, cm: centimeter, SD: standard deviation, min: minimum, max: maximum. Descriptive analyses were performed using mean and standard deviation, marked as * for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data.

As shown in Table 2, the patients' pre-operative hemoglobin level and erythrocyte distribution width (RDW) were correlated with FIGO staging, tumor size, myometrial tumor invasion, tumor differentiation, and tumor type (*P*<0.05 for each). Tumor invasion of myometrium was correlated with patient age, lymphocyte percentage, and NLR (*P*<0.05 for each), and lymphocyte percentage, NLR, alanine transaminase, and fasting blood glucose levels were significantly correlated with tumor differentiation (*P*<0.05 for each).

Table 2: Correlation analysis between tumor characteristics and patient findings

	FIGO stage r	FIGO stage P	Tumor Size r	Tumor Size P	Differentiation r	Differentiation P	Tumor Type r	Tumor Type P	Myometrial Invasion r	Myometrial Invasion P
Age*	0.13	0.08	-0.01	0.89	0.12	0.10	0.16	0.02	0.18	0.02
Duration of hospitalization (day)	0.06	0.41	0.01	0.84	0.2	0.009	0.07	0.36	0.06	0.39
Hemoglobin (g/dl)	-0.025	0.001	-0.15	0.04	-0.29	<0.001	-0.15	0.05	-0.22	0.004
Mean corpuscular volume (fl)	-0.08	0.34	-0.13	0.08	-0.1	0.20	-0.06	0.45	-0.1	0.19
Mean platelet volume (fl)*	0.06	0.43	-0.08	0.29	-0.12	0.11	0.001	0.98	0.01	0.84
Red cell distribution width (%)	0.16	0.03	0.2	0.008	0.27	<0.001	0.19	0.01	0.18	0.02
Neutrophil count (10^3/ml)	0.10	0.17	0.03	0.69	0.11	0.14	0.07	0.36	0.12	0.09
Lymphocyte count (10^3/ml)	-0.13	0.08	-0.08	0.32	-0.10	0.15	0.06	0.45	-0.11	0.14
Neutrophil percentage (%)*	0.1	0.19	0.03	0.66	0.13	0.09	0.02	0.98	0.12	0.11
Lymphocyte percentage (%)	-0.16	0.03	-0.09	0.25	-0.18	0.02	-0.01	0.89	-0.17	0.03
White blood cell (mcl)	0.1	0.19	0.02	0.79	0.1	0.21	0.09	0.24	0.08	0.29
Platelets (mcl)	0.08	0.28	0.02	0.81	0.08	0.30	0.02	0.81	0.05	0.47
Creatinine (mg/dl)	0.03	0.70	0.07	0.32	0.004	0.96	0.004	0.96	0.11	0.13
Alanine Transaminase (ALT) (u/l)	-0.25	0.001	-0.16	0.04	-0.21	0.004	-0.14	0.07	-0.12	0.09
Aspartate Transaminase (AST) (u/l)	-0.09	0.26	-0.07	0.33	-0.1	0.23	-0.07	0.38	0.003	0.97
Plasma glucose level (mg/dl)	-0.08	0.27	-0.03	0.69	-0.23	0.002	-0.09	0.24	-0.1	0.19
Fibrinogen	0.02	0.81	-0.14	0.07	0.01	0.90	-0.03	0.72	0.02	0.77
Neutrophil/Lymphocyte Ratio	0.13	0.08	0.08	0.29	0.15	0.05	-0.01	0.87	0.17	0.03
Platelet/Lymphocyte Ratio	0.18	0.02	0.10	0.15	0.17	0.02	-0.01	0.84	0.14	0.06

gr: gram, ml: milliliter, dl: deciliter, mcl: microliter, u: unit, r: correlation coefficient. *P*<0.05 was considered significant. (*: Pearson test, other Spearmen test)

As shown in Table 2, the type of endometrial tumors (Types 1 and 2) and the patient's age were correlated (*P*=0.02). Alanine transaminase enzyme was correlated with tumor size and FIGO stage, and lymphocyte percentage and PLR were correlated with the stage in endometrial cancers (*P*<0.05 for each).

The probability of tumoral invasion of more than ½ of the myometrium increases with age. Hemoglobin and RDW also affect myometrial invasion. As the percentage of lymphocytes increases, the possibility of myometrium invasion decreases. This reflects in the NLR and the PLR, creating a significant difference (*P*<0.05 for each) (Table 3).

Table 3: Comparison of laboratory parameters in terms of myometrial invasion

	Myometrial Invasion is less than ½ (n = 90) Mean (SD) Median (min-max)	Myometrial Invasion is more than ½ (n = 85) Mean (SD) Median (min-max)	P-value
Age*	59.7 (8.9)	62.9 (9.5)	0.02
Duration of hospitalization (day)#	7 (3-45)	7 (3-22)	0.39
Hemoglobin (g/dl)#	13.1 (7.4-15.6)	12 (6.3-17.3)	0.02
Mean corpuscular volume (fl)#	84.7 (58.6-94.5)	83.7 (63.8-97.5)	0.18
Mean platelet volume (fl)*	9.0 (1.3)	9.1 (1.1)	0.79
Red cell distribution width (%)#	13.7 (12-27.6)	14.4 (11.6-30.7)	0.02
Neutrophil count (10^3/ml)#	5.2 (1.6-15.4)	5.4 (2-24)	0.98
Lymphocyte count (10^3/ml)#	2 (0.4-8)	1.9 (0.3-4.1)	0.14
Neutrophil percentage (%)*	65.4 (10.6)	68.3 (11.9)	0.09
Lymphocyte percentage (%)#	26.7 (4.3-67.6)	23.7 (2.4-45.7)	0.03
White blood cell (mcl)#	8.290 (3.400-18.600)	8.770 (4.300-19.900)	0.29
Platelets (mcl)#	280.000 (136.000-553.000)	299.000 (13.5000-728.000)	0.47
Creatinine (mg/dl)#	0.79 (0.3-9)	0.82 (0.6-4.8)	0.13
Alanine Transaminase (ALT) (u/l)#	17 (6-62)	16 (1-114)	0.09
Aspartate Transaminase (AST) (u/l)#	20 (9-99)	21 (4-375)	0.97
Plasma glucose level (mg/dl)#	122 (76-286)	112 (67-258)	0.19
Fibrinogen#	344 (186-644)	350 (167-712)	0.05
Neutrophil/Lymphocyte Ratio#	2.4 (0.7-24.2)	2.8 (1-45.3)	0.03
Platelet/Lymphocyte Ratio#	136.9 (36.8-610)	153.4 (40.9-703.3)	0.05

Descriptive analyses were performed using mean and standard deviation, marked as * for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data. *P*-value <0.05 was considered significant. (*: t-test, #: Mann Whitney U)

Analysis according to the type of endometrial cancer is examined in Table 4. Patients with type 1 endometrial cancer constitute a significantly younger population than those with type 2 (*P*=0.048). While hemoglobin and lymphocyte percentage parameters measured before surgery are lower in patients with type 2 endometrial cancer, RDW, platelet/lymphocyte ratio, and neutrophil/lymphocyte ratios are higher (*P*<0.05 for all).

Table 4: Comparison of parameters in terms of endometrial cancer typing

	Type 1 Endometrial Cancer (n=142) Mean (SD) Median (min-max)	Type 2 Endometrial Cancer (n=33) Mean (SD) Median (min-max)	P-value
Age*	60.6 (9)	64.1 (10.2)	0.048
Duration of hospitalization (day)#	7 (3-45)	8 (4-22)	0.36
Hemoglobin (g/dl)#	12.7 (6.3-17.3)	11.8 (6.5-14.4)	0.05
Mean corpuscular volume (fl)#	84.4 (58.6-97.5)	83.6 (68.2-93.7)	0.46
Mean platelet volume (fl)*	9.1 (1.2)	9.1 (1.3)	0.82
Red cell distribution width (%)#	13.9 (11.6-30.7)	14.6 (12.6-28.1)	0.01
Neutrophil count (10^3/ml)#	5.2 (1.6-23.9)	5.4 (2-20)	0.36
Lymphocyte count (10^3/ml)#	2 (0.4-8)	2.1 (0.3-3.9)	0.44
Neutrophil percentage (%)*	66.8 (11.2)	66.7 (11.6)	0.96
Lymphocyte percentage (%)#	26.7 (4.3-67.6)	23.7 (2.4-45.7)	0.03
White blood cell (mcl)#	8.290 (3.400-18.600)	8.770 (4.300-19.900)	0.29
Platelets (mcl)#	280.000 (136.000-553.000)	299.000 (135.000-728.000)	0.47
Creatinine (mg/dl)#	0.79 (0.3-9)	0.82 (0.6-4.8)	0.13
Alanine Transaminase (ALT) (u/l)#	17 (6-62)	16 (1-114)	0.09
Aspartate Transaminase (AST) (u/l)#	20 (9-99)	21 (4-375)	0.97
Plasma glucose level (mg/dl)#	122 (76-286)	112 (67-258)	0.19
Fibrinogen#	344 (186-644)	350 (167-712)	0.77
Neutrophil/Lymphocyte Ratio#	2.4 (0.7-24.2)	2.8 (1-45.3)	0.03
Platelet/Lymphocyte Ratio#	136.9 (36.8-610)	153.4 (40.9-703.3)	0.05

Descriptive analyses were performed using mean and standard deviation, marked as * for normally distributed data, and median and minimum-maximum values (median (min-max)) for non-normally distributed data. *P*-value <0.05 was considered significant. (*: t-test, #: Mann Whitney U)

We divided the patients into three groups according to differentiation: Grade 1 indicated high differentiation, Grade 2, moderate differentiation and Grade 3, poor differentiation. As shown in Table 5, Hb, MPV, RDW, ALT, Fasting blood glucose,

Lymphocyte percentage, NLR, and PLR significantly differed between the groups ($P<0.05$ for each). Post-hoc evaluation of the groups in pairs showed that MPV, Hb, lymphocyte percentage, fasting blood glucose, and PLR significantly differed between grade 1 and 2 tumor groups ($P<0.05$ for each), while only hemoglobin value significantly differed between Grade 1 and Grade 3 groups ($P=0.01$).

Binary logistic regression was used to determine the independent predictors of more than ½ thickness myometrial invasion. Accordingly, as NLR increased, so did the chances of more than ½ thickness myometrial tumor invasion ($P=0.05$) (Table 6).

Table 5: Comparison of laboratory parameters in terms of tumor differentiation

	Grade 1 (n=92) Mean (SD) Median (min-max)	Grade 2 (n=58) Mean (SD) Median (min-max)	Grade 3 (n=25) Mean (SD) Median (min-max)	P-value	P-value Grade1 & Grade2	P-value Grade1 & Grade3
Age*	60.4 (8.2)	61.8 (10.4)	63.4 (10.9)	0.30		
Duration of hospitalization (day)#	7 (3-45)	8 (4-33)	7 (4-22)	0.12		
Hemoglobin (g/dl)#	13 (6.3-17.3)	12.1 (6.5-15.1)	11.7 (8.1-14)	0.001	0.02	0.01
Mean corpuscular volume (fl)#	84.7 (60.7-97.5)	83.8 (58.6-94.3)	83 (68.2-98)	0.45		
Mean platelet volume (fl)*	9.3 (1.2)	8.8 (1.18)	9.2 (1.28)	0.02	0.02	0.959
Red cell distribution width (%)#	13.6 (11.6-31.7)	14.3 (12.6-27.1)	14.8 (12.6-28.1)	0.002	0.23	0.11
Neutrophil count (10³/ml)#	5 (2.5-15.4)	5.4 (1.6-23.9)	6.3 (2-20)	0.31		
Lymphocyte count (10³/ml)#	2 (0.5-8)	1.9 (0.4-5.5)	2.1 (0.3-3.9)	0.07		
Neutrophil percentage (%)*	65.6 (10.8)	68.3 (11.7)	67.9 (11.9)	0.29		
Lymphocyte percentage (%)#	27.9 (4.2-67.6)	23.4 (3.6-47.2)	21.9 (2.4-39.9)	0.03	0.04	0.36
White blood cell (mcl)#	8.1 (5-18.6)	8.3 (3.4-19.9)	9.6 (4.3-24.2)	0.41		
Platelets (mcl)#	285 (135-553)	282 (181-685)	300 (162-725)	0.59		
Creatinine (mg/dl)#	0.81 (0.3-9)	0.78 (0.5-1.6)	0.8 (0.6-3.2)	0.98		
Alanine Transaminase (ALT) (u/l)#	19 (1-64)	15 (5-44)	13 (5-114)	0.02	0.07	0.98
Aspartate Transaminase (AST) (u/l)#	21 (4-85)	21 (8-375)	19 (11-135)	0.43		
Plasma glucose level (mg/dl)#	125 (76-282)	109 (78-286)	101 (67-264)	0.01	0.03	0.07
Fibrinogen#	346 (176-654)	344 (189-712)	355 (167-491)	0.82		
Neutrophil/Lymphocyte Ratio#	2.2 (0.7-24.2)	2.8 (0.9-25.6)	2.7 (1.1-45.3)	0.05	0.17	0.62
Platelet/Lymphocyte Ratio#	127.8 (36.8-494)	156.9 (51.8-620)	142.3 (67.1-703.3)	0.01	0.04	0.52

Descriptive analyses were performed using mean and standard deviation, marked as * for normally distributed data, and median and minimum-maximum values (median (min-max) for non-normally distributed data. *P*-value <0.05 was considered significant. (*: One Way ANOVA, #: Kruskal Wallis) Tukey tests were used in cases where variances were homogeneously distributed from post hoc tests and Games-Howell tests were used in cases where they were not homogeneously distributed for the double group analysis of the results that were significant in multiple analysis. Homogeneity of variances was evaluated by Levene test.

Table 6: Binary logistic regression analysis results in terms of prediction of myometrial Invasion

Myometrial Invasion	Wald	OR	95% CI	P-value
Hemoglobin (g/dl)	3.65	0.869	0.714-0.924	0.05
Neutrophil/Lymphocyte Ratio	2.49	1.069	0.886-0.940	0.05

GA (95%); confidence interval; OR: odds ratio. Wald: test statistic value. Binominal logistic regression was used because the dependent variable consists of 2 groups. The reference group was the one with less than ½ myometrial invasion. Variables with *P*<0.25 in univariate analysis were included in the multivariate analysis. The Backward LR method was used in binary analysis. In the Hosmer-Lemeshow test, *P* is >0.05 and the models fit well with the data.

Discussion

The impact of inflammation in various cancers, including cancer initiation, development, progression, and metastasis, has recently been described [24]. Since the association between cancer and inflammation was first reported, many studies have been conducted on this subject. Today, we know that many cells we evaluate with complete blood count play a role in the chronic inflammatory pathway. However, the relationship between cancer and inflammation is frequently mentioned in the literature. Studies on this are gradually increasing and becoming remarkable [25–27].

Endometrial carcinoma is the most common malignancy among gynecological neoplasms. Studies show that proinflammatory cytokines could stimulate aromatase activity in the adipose tissue, increasing estrogen production and bioavailability. Inflammatory markers can be elevated in endometrial cancer patients [28, 29].

In studies conducted on patients with endometrial cancer, various complete blood parameters such as WBC count, PDW, MPV, platelet, and NLR are higher. There are even reports that some of these values affect tumor stage, differentiation, and lymph node invasion. In other words, complete blood parameters can be a useful diagnostic or screening tool in patients with endometrial cancer [30–33]. Kemal et al. defined the association between red blood cell distribution width and endometrial cancer [34]. Takahashi R. et al. found that thrombocytosis and neutrophilia are associated with poor prognosis in stage 3 and 4 endometrial cancer patients [35]. Njølstad et al. [36] and Luomaranta et al. [37] determined that pre-operative anemia, leukocytosis, or thrombocytosis is related to endometrial cancer and its poor prognosis with distant metastasis. Temur et al. [38] found that pre-operative NLR and PLR values are essential in endometrium cancer in predicting poor prognostic factors, including advanced-stage disease, deep myometrial invasion, cervical and nodal involvement. Zhou et al. [39] stated that pre-operative higher fibrinogen values can predict possible lymphovascular invasion in endometrial cancer.

Our study determined that some of the complete blood parameters we examined pre-operatively may be related to endometrial cancer, stage of the disease, and prognostic factors. The tumor stage may be increased with decreased hemoglobin value and lymphocyte percentage, and increased red cell distribution width. It may also indicate an increased risk of more than ½ thickness myometrial invasion and poor differentiation. Tumor myometrium invasion may increase with higher NLR and PLR. Fittingly, these two parameters were lower in well-differentiated tumors. We also found that more than ½ thickness myometrial invasion is more likely with increased plasma fibrinogen levels. Mean platelet volume levels significantly differed in terms of tumor differentiation among the three groups. There were few significant studies in which MPV values were associated with endometrial cancer and advanced stage. However, this is perhaps the first study to demonstrate the relationship between MPV and the degree of tumor differentiation.

In our study, lower hemoglobin values and higher NLR were highly predictive of more than ½ thickness myometrial invasion, which is one of the poor prognostic factors in endometrial carcinoma. Studies in the literature show the relationship of endometrial cancer with inflammatory markers and its poor prognostic status in the presence of anemia, both of which were supported by our results. We think that our study will contribute to the literature in terms of the multifaceted effects of inflammation on endometrial cancer.

Evaluation of the patients according to Bokhman's histomorphological classification showed that RDW, NLR, and PLR values were higher in patients with type 2 endometrial cancer, while hemoglobin and lymphocyte percentages were lower. This may give the surgeon an idea, especially in patients who are scheduled for frozen examination or lymph node dissection during surgery. Analyses with more patients are needed.

The most important limitations of this study include its retrospective single-center design and relatively small patient size. However, the present study is the first to report the usability of the hemoglobin, neutrophil, and lymphocyte count for detecting myometrial invasion of endometrial cancer and type of disease.

Conclusion

Our study showed the potential predictive and prognostic roles of complete blood count parameters in endometrium cancer. Hemoglobin, RDW, NLR, lymphocyte percentage, and MPV were significant prognostic parameters of endometrial cancer. As complete blood count levels can be routinely determined pre-operatively, these low-cost and readily available parameters may be novel and promising markers to predict poor prognosis. However, comprehensive studies on different histological subtypes or gynecological cancers are necessary to further determine these tests' use for malignancies.

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Relationship between vitamin D receptor gene polymorphisms and vitamin D levels in children

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Abstract

Background/Aim: Vitamin D exerts its effects in the body through its receptors. Polymorphisms in vitamin D Receptor (VDR) gene are known to cause certain diseases and affect vitamin D levels. In this study, we planned to examine the relationship between vitamin D levels and Vitamin D gene polymorphisms among children.

Methods: The study group included 124 healthy children living in the same region. Vitamin D (VitD), Parathyroid Hormone (PTH), Alkaline phosphatase (ALP), Calcium (Ca), Phosphorus (P) and Magnesium (Mg) were examined in the blood samples taken. In terms of measured Vitamin D levels, children were divided into group 1 (Vitamin D < 20 ng/mL) and group 2 (Vitamin D ≥ 20 ng/mL). Deoxyribonucleic Acid (DNA) was isolated from the serum sample, VDR ApaI and TaqI polymorphisms were determined by Polymerase Chain Reaction (PCR) method, and comparisons were made between groups.

Results: The overall mean age of the children included in the study was 8.11 (4.98) years. The mean ages of participants in Groups 1 and 2 were 9.38 (4.87) years and 6.38 (4.62) years, respectively (P=0.091). The mean vitamin D levels of Groups 1, 2 and overall were 13.82 (3.29) ng/mL, 33.96 (20.47) ng/mL, and 23.49 (21.54) ng/mL, respectively (P=0.509). The two groups were similar in terms of serum ALP, PTH, Ca, Mg and P levels (P>0.05 for all). VDR polymorphisms were found to have no effect on Vitamin D levels.

Conclusion: In our study, no relationship was found between the genotypes of ApaI and TaqI polymorphisms and Vitamin D levels. This study is important in terms of remarking the fact that Vitamin D deficiency is still a public health problem and its contributions to VDR gene polymorphism research.

Keywords: Vitamin D, Vitamin D receptor, Polymorphism

Introduction

Vitamin D is mainly synthesized in the skin by way of ultraviolet-B (UV-B) rays from sunlight, but also partially ingested from vegetable and animal foods. It is activated in our body after being hydroxylated in the liver first, then the kidney, and besides its many effects in our body, it mainly affects the calcium (Ca^{+2}) metabolism [1,2]. It was demonstrated that Vitamin D receptor (VDR) resides in the immune system, as well as many tissues such as blood cells and the central nervous system [3].

The function of Vitamin D in our body is mediated by VDR. Many polymorphisms were identified in studies examining the VDR gene, i.e., ApaI, TaqI, FokI and BsmI polymorphisms [4]. There are studies investigating the relationship between Vitamin D levels and VDR gene polymorphisms, and different results have been obtained in different populations [5-9].

In our study, we aimed to determine the frequency of VDR Apa and Taq polymorphisms, their genotype typology in healthy children and relationship with serum vitamin D levels.

Materials and methods

A total of 124 healthy children aged 12 months-18 years who visited Kafkas University Faculty of Medicine, General Pediatrics Outpatient Clinic for routine checkup, had no complaints and normal physical examination findings, had not used daily or depot vitamin D preparations within the last 3 months and not lived in any place other than the place of residence within the last 6 months were included in this study. A total of 72 children with vitamin D insufficiency, deficiency and severe deficiency based on blood samples obtained in routine examinations, and 52 children with normal vitamin D values were included in the study on a voluntary basis.

Approval for this thesis study was obtained from the Ethics Committee of Kafkas University Faculty of Medicine with the decision number 11 of the document dated 31.10.2018 and numbered 177. Informed consent was obtained from each participating child and their parents by providing detailed information about the study.

Those with a condition requiring hospitalization, without an informed consent form obtained from their parents and those who did not want to participate in the study, those with a known chronic disease, clinical complaints of Vitamin D deficiency or excess, abnormal physical examination findings, those who have used depot or daily doses of Vitamin D preparations within the last 3 months, and those who have lived in another region within the last 6 months were excluded from the study. Ca^{+2}, P, ALP, Mg and PTH levels were examined simultaneously with vitamin D levels.

After the biochemical parameters were examined, the remaining serum samples were stored in Eppendorf tubes in a -20°C deep freezer until genetic analysis. DNA was isolated from stored samples and Apal and Taql gen polymorphisms were studied (Figure 1, 2).

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 20 was used for the analysis of the data. Two groups were formed in terms of Vitamin D level: Group 1 included children with Vitamin D < 20 ng/mL and group 2 included those with Vitamin D ≥ 20 ng/mL. Visual graphics (Histogram) and the Kolmogorov-Smirnov test were used to check whether parameters complied with normal distribution. The relationship between the genotype and allele distributions of TaqI and ApaI polymorphisms and Vitamin D levels of the two groups was evaluated by Pearson's Chi-Square test. The vitamin D results of the groups with Apal and Taql polymorphisms were evaluated with the ANOVA test. $P<0.05$ values were considered statistically significant in all tests.

Results

The mean age of 124 healthy children participating in the study was 8.11 (4.98) years. Groups 1 and 2 (9.38 (4.87) years vs. 6.38 (4.62) years) and females and males (8.47 (5.33) years vs. 7.86 (4.74) years) were similar in terms of age ($P=0.091$ and $P=0.603$, respectively). There were 36 females and 36 males in Group 1, and 14 females and 38 males in Group 2.

Figure 1: A: Cutting with ApaI among children with Vitamin D < 20ng/mL, B: Cutting with ApaI among children with Vitamin D ≥20ng/ml
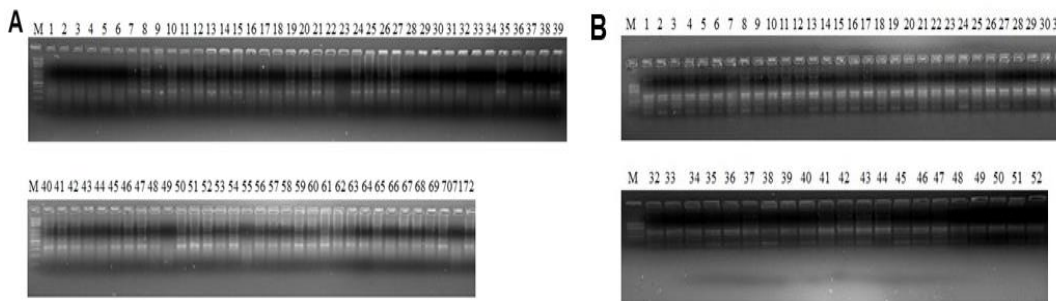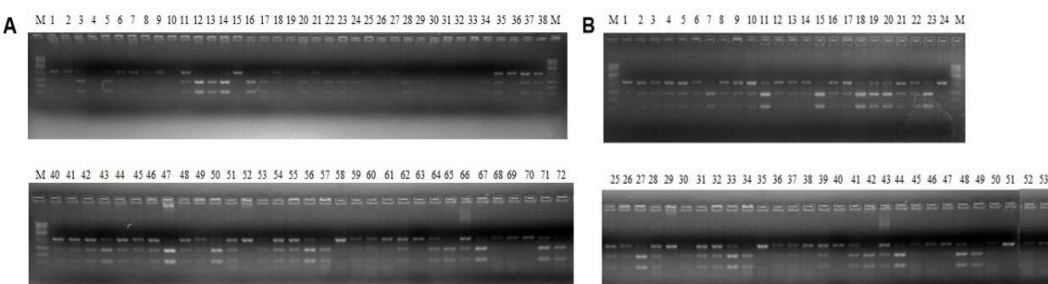

Figure 2: A: Cutting with TaqI among children with Vitamin D < 20ng/mL, B: Cutting with TaqI among children with Vitamin D ≥ 20 ng/mL

The mean vitamin D levels in Groups 1, 2 and overall were 13.82 (3.29) ng/ml, 33.96 (20.47) ng/ml, and 23.49(21.54) ng/ml, respectively, with no significant difference between the groups (P=0.509). The lowest and highest vitamin D level among all children were 5 ng/ml and 116 ng/ml, respectively. The mean vitamin D levels of male and female children were 24.73 (17.64) ng/ml, and 18.62 (14.69) ng/ml, respectively (P<0.001) (Table 1).

In terms of ApaI polymorphism, 32% had AA genotype, 57% had Aa genotype, and 11% had aa genotype. For TaqI polymorphism, 42% had TT genotype, 48% had Tt genotype, 10% had tt genotype (Table 2).

Table 1: Mean 25(OH) D3 across all population and genders

Group	25(OH)D3 Average	n	P-value
Vitamin D <20 ng/mL	13.82 (3.29)	72 (58%)	
Vitamin D≥20ng/mL	33.96 (20.47)	52 (42%)	0.509
All Population	23.49 (21.54)	124 (100%)	
Males (all population)	24.73 (17.64)	74 (59.7%)	
Females (all population)	18.62 (14.69)	50 (40.3%)	0.001

Table 2: Distribution of ApaI, TaqI polymorphism genotypes among the groups and overall

	Vitamin D <20ng/mL (n=72)	Vitamin D ≥20ng/mL (n=52)	P-value	All Population (n=124)	Total %	Girl (n=50)	Boy (n=74)	P-value
ApaI								
AA	25 (35%)	15 (29%)		40	32	18	22	
Aa	40 (55%)	31 (60%)	0.777	71	57	28	43	0.656
aa	7 (10%)	6 (11%)		13	11	4	9	
TaqI								
TT	31 (43%)	21 (40%)		52	42	19	33	
Tt	34 (47%)	25 (48%)	0.927	59	48	28	31	0.175
tt	7 (10%)	6 (12%)		13	10	3	10	

In Group 1, 35% had AA, 55% had Aa, 10% had aa, 43% had TT, 47% had Tt, and 10% had tt genotypes. The rates of AA, Aa, aa, TT, Tt and tt genotypes in Group 2 were 29%, 60%, 11%, 40%, 48% and 12%, respectively (Table 2).

Vitamin D levels among these genotypes were as follows: 19.58 ng/mL in AA, 22.94 ng/mL in Aa, 26.85 ng/mL in aa, 20.69 ng/mL in TT, 24.10 ng/mL in Tt, and 20.23 ng/mL in tt. Vitamin D levels did not significantly differ according to ApaI and TaqI genotypes (P=0.348, P=0.509, respectively) (Table 3).

Table 3: Relationship between Vitamin D level and ApaI and TaqI polymorphisms genotypes

	AA	Aa	aa	P-value
Vitamin D(ng/mL)	19.58 (10.38)	22.94 (17.13)	26.85 (27.45)	0.348
	TT	Tt	tt	
	20.69 (12.66)	24.10 (20.32)	20.23 (12.51)	0.509

Discussion

According to studies conducted in different age groups of many societies, Vitamin D insufficiency and deficiency are at a remarkable level all over the world [10-13]. Research in Turkey showed that rates of overall vitamin D deficiency and insufficiency were 51.8% and 20.7%, respectively. The mean vitamin D level in deficient individuals was 18.7 (6.8) ng/mL in Erzurum, and 52% of children aged between 2-4 years, 62.5% of children aged between 5-8 years and 63% of children aged between 9-12 years were vitamin D deficient [14,15].

In the present study, mean Vitamin D levels were 23.49 ng/mL. Among 124 children, Vitamin D levels were below 20 ng/mL in 72 (58%) cases and within normal limits in 52 (42%). None had severe deficiency or intoxication, while vitamin D levels of 34.7% were deficient, 23.4% were insufficient, 41.4% were normal, and 0.8% were excess (Table 4). In this respect, this study was compatible with other studies conducted in our region in terms of Vitamin D deficiency/insufficiency.

Table 4: Overall Distribution of Vitamin D

	n	%
Severe Deficiency (<5 ng/mL)	0	0
Deficiency (5-15 ng/mL)	43	34.7
Insufficiency (15-20 ng/mL)	29	23.4
Normal (20-100 ng/mL)	51	41.1
Excess (100-150 ng/mL)	1	00.8
Intoxication (>150 ng/mL)	0	0

The females included in our study had significantly lower vitamin D levels compared to females. Vitamin D deficiency affects females more often because of the traditional lifestyle in Turkey. In a study conducted with 14.091 participants in USA to set forth the correlation between Vitamin D levels and gender, the mean levels of vitamin D among male and female children were 31.37 ng/mL and 28.72 ng/mL, respectively, which significantly differed [16]. In a study conducted in Kocaeli region in Turkey, the 25-OH level in 50% of female students was below 10 ng/mL, while this rate was between 3 and 13% in other students [17]. Both in the present study and in studies conducted in Turkey and other countries, vitamin D levels of females are lower compared to males.

Genetic factors controlling vitamin D levels play an important role in vitamin D deficiency. Many polymorphisms were identified in studies conducted on the VDR gene, i.e., ApaI, TaqI, FokI and BsmI [18]. In their study on FokI, ApaI and TaqI polymorphisms in the VDR Gene among 100 healthy Turkish individuals, Dayangaç et al. [19] documented the rates of AA, Aa, aa, TT, Tt and tt as 30%, 55%, 15%, 35%, 49%, and 16%, respectively. In another polymorphism study conducted with a healthy population in India, TT, Tt, tt, AA, Aa and aa genotypes were 49%, 40%, 11%, 36%, 44% and 20%, respectively [20].

In a VDR ApaI and TaqI polymorphism study conducted with a healthy population in Iran, AA, Aa, aa, TT, Tt and tt genotypes for ApaI and TaqI were 42%, 47%, 10%, 36%, 58%, and 6%, respectively [21]. Our results were like those obtained by Dayangaç et al. [19]. At this point, it is evident that the study population reflects the genetic profile of Turkey and demonstrates similarities in terms of polymorphism and genotype rates with the studies performed in the healthy population in various countries.

There are many studies regarding the correlation between VDR gene polymorphisms and vitamin D levels in the world and in Turkey; nevertheless, the results were inconsistent with each other. The relationship between Vitamin D levels and polymorphisms in the VDR gene was demonstrated in certain studies [5-9, 22-25]. Contrarily, studies with no evident correlation on this issue were conducted both abroad and in Turkey. For example, no significant difference was found between Vitamin D levels with respect to TaqI polymorphisms in India [26]. VDR polymorphisms (BsmI, TaqI, ApaI) were not associated with Vitamin D levels in patients diagnosed with Graves' disease in Egypt [27]. In the studies conducted by Maalmi et al. [28] on children with asthma in Tunisia, Elrawi et al. [29] on patients with hypothyroidism, and Faghfouri et al. [30] on patients with autoimmune thyroiditis in Iran, no relationship was found between Vitamin D levels and VDR gene polymorphisms. In Turkey, no significant association was found between Vitamin D levels and FokI polymorphism among major depression patients [31]. In a study evaluating 84 pediatric patients with a diagnosis of Hashimoto's Thyroiditis, VDR polymorphisms and vitamin D levels were not related [32, 33].

This study demonstrated that ApaI and TaqI VDR gene polymorphisms do not pose a risk for Vitamin D deficiency and insufficiency, similar to studies that did not detect a relationship between VDR gene polymorphisms and vitamin D levels in the literature.

Limitations

Although VDR has different genetic polymorphisms, this study was conducted with two. The failure to include other polymorphisms can be considered as the limitation of this study.

Conclusion

Vitamin D deficiency is still an important societal problem today. The study group only includes healthy children and has a wide age range (12 months-18 years). The study population is sufficient compared to other studies, and it is the first VDR gene polymorphism study conducted in the relevant region. In light of all these data, it is thought that the study will contribute to further studies to be conducted in this regard.

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Comparison of laparoscopic and conventional Graham's omentopexy in peptic ulcer perforation: A single center experience

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Abstract

Background/Aim: In recent years, laparoscopic repair has become common in the treatment of peptic ulcer perforation (PUP). In this study, we aimed to compare the advantages and disadvantages of laparoscopic and conventional graham omentopexy in the treatment of peptic ulcer perforation (PUP).

Methods: The files of the patients who underwent laparoscopic and conventional graham omentopexy were reviewed in this retrospective cohort study. The two groups were compared in terms of age, gender, comorbidities, ASA scores, location and diameter of perforation, Mannheim Peritonitis Index (MPI), operation times, VAS scores (4th and 24th hour), oral intake, flatus, length of hospital stay, postoperative complications, morbidity, and mortality.

Results: A total of 192 cases were included in the study, with 123 patients in the Laparoscopy Group and 69 patients in the Conventional Group. In the Laparoscopy Group, earlier oral intake, earlier bowel movements, less pain, shorter length of hospitalization, less pulmonary and total complications, and fewer secondary interventions were observed ($P=0.001$, $P=0.001$, $P=0.001$, $P=0.037$, $P=0.009$, $P=0.039$, respectively). In the Conventional Group, the mean operation time was significantly shorter ($P=0.002$). Other findings were similar.

Conclusion: We observed many advantages of laparoscopic repair in the treatment of peptic ulcer perforation. Longer operation time was the only disadvantage. Based on our results, we believe that laparoscopic approach is safe and superior to conventional surgery in the treatment of peptic ulcer perforation.

Keywords: Laparoscopy, Peptic ulcer perforation, Graham's omentopexy, Postoperative complications, Minimally invasive surgery

Introduction

Peptic ulcer disease (PUD) is commonly seen worldwide, with an incidence between 0.03%-0.19%. Approximately 50% of the global population is infected with *Helicobacter pylori*, which is a risk factor for the development of peptic ulcer. The incidence of H. Pylori infection decreased after the use of proton pump inhibitors (PPI). Due to the success of medical treatment, elective surgical treatment is almost abandoned. However, there was no decrease in the frequency of perforation, hemorrhage, and obstruction, which are among the complications of peptic ulcer [1-4]. Peptic ulcer perforation (PUP) is an important indication for emergency surgery, with 2-10% complication in peptic ulcer disease [5]. PUP is the second most common abdominal organ perforation that requires urgent surgery after appendicitis perforation [6].

Simply closing the PUP with an omental patch has become the preferred approach [7, 8]. Since 1990, laparoscopic repair is widely accepted in the effective treatment of PUP [9]. The laparoscopic approach overcomes the disadvantages of traditional open repair, including large upper abdominal incision, wound infection and separation, prolonged ileus and pulmonary complications, delayed healing times, and late complications such as incisional hernia [10-12]. However, the duration of laparoscopic surgery in PUP is generally longer than that of conventional surgery [13].

In this study, we aimed to compare the advantages and disadvantages of laparoscopic and conventional graham's omentopexy in PUP treatment.

Materials and methods

Patient

The files of 202 patients operated for PUP between January 2015 and January 2020 were analyzed retrospectively. Patients older than 18 years without previous abdominal surgery or septic shock, those with mean arterial pressure >65 mm Hg and benign ulcer perforation were included in the study. Patients with perioperative septic shock, tumor-induced perforation, mean arterial pressure <65 mm Hg, previous abdominal surgery, and patients requiring conversion to conventional surgery in the laparoscopy group (LG) were excluded from the study. A total of 192 patients were included in the study after exclusion criteria, 123 of which underwent laparoscopic and 69 of which underwent Graham's omentopexy, the routinely used method in PUP in our clinic. The two groups were compared in terms of age, gender, comorbidities, body mass index (BMI), American Society of Anesthesiology (ASA) scores, location and diameter of perforation, Mannheim Peritonitis Index (MPI), operation times, VAS scores (4th and 24th hour), oral intake, flatus, length of hospital stay, postoperative complications, morbidity, and mortality. The choice of laparoscopic vs conventional technique was at the surgeon's discretion.

Surgical technique

All surgeries were performed under general anesthesia. In laparoscopic Graham omentopexy technique, the screen was placed to the patient's right posterolateral side. The patient was placed in reverse Trendelenburg position and the surgeon performed the operation between the patient's legs. A 10 mm horizontal incision was made sub-umbilically. Veress needle was inserted, and CO2 was insufflated until the intraperitoneal pressure reached 12 mmHg. A 30-degree camera was inserted through the trocar and two 5 mm working trocars were inserted in the right and left upper quadrants, on the midclavicular line. After the abdomen was explored, the perforation area was exposed. If the perforation area could not be exposed, methylene blue was administered from the nasogastric tube to identify its location. Then, two absorbable sutures (2/0 vicryl) were placed parallel to the location of perforation. To prevent the placed sutures from cutting through the ulcer site, at least 1 cm intact tissue was left between the sutures. The omentum was placed between these two sutures, which were knotted intracorporeally. Laparoscopic lavage was performed in four quadrants of abdomen and a drain was placed in the near the omentopexy site.

In the conventional Technique, a midline supraumbilical incision was made to enter the abdomen. After the abdomen was explored, the perforation area was exposed. As in the laparoscopic technique, two absorbable sutures (2/0 vicryl) were placed parallel to the perforation area, the omentum was placed between these two sutures and knotted. Four quadrants of the abdomen were washed out with physiological saline and aspirated. A drain was placed in the near the omentopexy site.

Postoperative medical follow-up

In the postoperative period, proton pump inhibitors were administered routinely to the patients for 4 weeks. Control upper GIS endoscopies were performed at the first postoperative month. Biopsies were obtained from the edges of the ulcer to exclude malignancy, especially in patients with pre-pyloric ulcers. In addition, the presence of H. pylori was investigated by endoscopic biopsy in all cases, and eradication was performed in H. pylori positive patients.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) 24.0 program was used for statistical analysis. Mann-Whitney U and descriptive statistical methods were used for binary group comparisons of normally distributed parameters. Fisher's test and Pearson Chi-Square test were used to analyze qualitative data and developing complications. The results were considered statistically significant at $P<0.05$ and $P<0.01$.

Results

Between January 2015-2020, 202 patients were operated on due to PUP. Seven patients who met the exclusion criteria in the conventional group (CG) and three patients who required conversion to conventional laparotomy in the laparoscopy group (LG) were excluded from the study. Two of the seven patients excluded from the CG had tumor perforation and a distal subtotal gastrectomy was performed. Two patients had previously undergone abdominal surgery. Three patients were in the septic shock and their mean arterial pressures were <65 mmHg. All surgeons decided to treat these patients with conventional surgery, and they were excluded from the study so that the groups were homogenous when comparing the two techniques. Our conventional conversion rate was 2.38% (3/126). In all three patients, the reason for conversion was difficulty of exploration due to intra-abdominal adhesions. A total of 192 patients were included in the study after implementation of the exclusion

criteria, with 123 in LG, and 69 in CG. There were 105 males and 18 females in the LG, and 52 males and 17 females in the CG. There was no significant difference between the two groups in terms of demographic data, BMI, ASA scores and comorbidities ($P>0.05$) (Table 1).

Table 1: Demographic data and comorbidities

	Laparoscopic group (n:123)	Conventional group (n:69)	P-value
Sex			0.614
Female	18 (14.6 %)	12 (17.4 %)	
Male	105 (85.4 %)	57 (82.6 %)	
Mean Age (SD)	40.91 (16.75)	46.59 (19.41)	0.07
Min/max(med)	17-82 (37)	18-87 (47)	
Mean BMI (SD)	27.52 (2.87)	26.10 (2.33)	0.618
Comorbidity			
Yes	34 (27.6 %)	25 (36.3 %)	0.616
No	89 (72.4 %)	44 (63.7 %)	
Charlson comorbidity index (SD)	2.72 (02)	2.79 (0.3)	0.924
ASA Score			
1	17 (13.8 %)	13 (18.8 %)	
2	76 (61.8 %)	29 (42.1 %)	0.068
3	23 (18.7 %)	21 (30.4 %)	
4	7 (5.7 %)	6 (8.6 %)	

Location and diameter of perforation and MPI were similar between the two groups ($P>0.05$). However, the mean physiological saline volume used in peritoneal lavage was higher in the CG ($P=0.001$), and the mean operative time was shorter ($P=0.002$) (Table 2).

Table 2: Intra-operative and post-operative data

	Laparoscopic group (n=123)	Conventional group (n=69)	P-value
Size of perforation			
0-1 cm	81 (65.8 %)	38 (55 %)	0.673
1-2 cm	42 (34.2 %)	31 (45 %)	
Location of perforation			
Pre-pyloric	29 (23.57 %)	14 (20.28 %)	0.626
Post-pyloric	94 (76.43 %)	55 (79.72 %)	
Mean MPI (SD)	17.36 (4.61)	18.59 (5.04)	0.133
Min/max(med)	10-32(16)	10-31(17)	
Mean Volume of lavage (ml) (SD)	1820 (836)	2810 (1385)	0.001
Min/max(med)	1000-3000(2000)	1000-10000(3000)	
Mean Operating time (SD)	100.51 (30.70)	86.39 (27.84)	0.002
Min/max(med)	36-185(99)	40-160(80)	
Mean VAS 4th score (SD)	5.19 (1.29)	5.31 (1.28)	0.298
Min/max(med)	2-9 (5)	2-8(5)	
Mean VAS 24th score (SD)	3.20 (1.10)	4.53 (1.31)	0.001
Min/max(med)	1-6 (3)	2-8 (4)	
Mean Oral intake (day) (SD)	1.024 (0.20)	1.52 (0.96)	0.001
Min/max(med)	1-3 (1)	1-6 (1)	
Flatus (SD)	1.83 (0.68)	2.91 (1.26)	0.001
Min/max(med)	1-3 (2)	1-8 (3)	
Mean Length of hospital stay (SD)	3.45 (1.23)	5.55 (6.76)	0.001
Min/max(med)	2-12 (3)	2-50 (3)	

VAS scores were measured at the postoperative 4th and 24th hours. The 24th hour VAS score was lower in the LG compared to the CG ($P=0.001$) (Table 2).

Oral feeding began in 1.024 (0.20) days in the LG and 1.52 (0.96) days in the CG ($P<0.001$). On average, gas passage was observed in 1.83 (0.68) days and 2.91 (1.26) days in the LG and CG, respectively, indicating significantly earlier initiation of bowel movements in the LG ($P=0.001$). The mean length of hospital stay was shorter in the LG ($P=0.001$) (Table 2).

Postoperatively, superficial wound infection was observed in 7 (5.6%) patients in the laparoscopic group, and 10 (14.5%) patients in the CG ($P=0.039$). Pulmonary complications were observed less in the laparoscopic group ($P=0.037$). Postoperative leakage, separation of fascia, intra-abdominal abscess and prolonged ileus incidence were similar in both groups. However, when the total complications were compared excluding

the superficial wound infection, 10 complications were observed in the LG and 19 were seen in the CG ($P=0.016$) (Table 3).

Re-operation was performed in 3 patients in the LG and 6 patients in the CG. All patients in the LG were re-operated due to postoperative leakage, while four of the six patients in the open group were re-operated due to postoperative leakage and two, due to separation of the fascia. Although the number of patients re-operated in the CG was higher, there was no significant difference ($P=0.073$) (Table 3).

Table 3: Post-operative Complications

	Laparoscopic group (n=123)	Conventional group (n=69)	P-value
Superficial wound infection	7 (5.6 %)	10 (14.5 %)	0.039
Intraabdominal abscess	4 (3.25 %)	4 (5.8 %)	0,461
Separation of fascia	0	2 (2.9 %)	0.128
Prolonged ileus	0	2 (2.9 %)	0.128
Leakage	3 (2.43 %)	4 (5.79 %)	0.253
Pulmonary complications	3 (2.43 %)	7 (10.14 %)	0.037
Total complications	10 (8.13 %)	19 (27.50 %)	0.016
Interventional drainage	4 (3.25 %)	4 (5.8 %)	0.461
Re-operation	3 (2.43 %)	6 (8.69 %)	0.073
Total Secondary Intervention	7 (5.7 %)	10 (14.49 %)	0.039
Mortality	0	2 (2.9 %)	0.128

Interventional radiology placed drains for intra-abdominal abscesses in four patients in each group ($P=0.461$) (Table 3). The rate of secondary intervention was higher in the CG ($P=0.039$) (Table 3).

While there was no mortality in the LG, 2 (2.89%) mortalities occurred in the conventional group. Two patients who died were ASA 4E and followed up in the intensive care unit after surgery. One of these patients had a postoperative leak, while the other patient had no intra-abdominal complications. There was no significant difference in mortality between the two groups ($P=0.128$) (Table 3).

In the control endoscopies performed in the 1st month postoperatively, no evidence of malignancy was observed in any patient.

Discussion

PUP incidence changes between 1.5-3%, lifetime prevalence is 5% and mortality rate is between 1.3-20% [14]. It is a serious complication requiring urgent intervention, in which treatment consists of closing the perforation area. Conventional repair was the standard treatment for the past 10 years. In recent years, with advances in minimally invasive surgery, laparoscopic approach is increasingly preferred for the treatment of acute abdomen. Laparoscopic repair is widely used in PUP treatment today [15-16]. In the literature, simple closure, standard Graham's omentopexy, modified Graham's omentopexy, and fibrin glue closure techniques were used in the laparoscopic treatment of PUP [15, 17-21].

In this study, the demographic data were similar, but most patients were male in both groups. There were 85% males in the LG and 82% males in the CG. The results of many studies are similar to ours, and we observed that the patients operated with PUP were mostly male in the past studies [19, 22 ,23-25].

In our study, there was no difference between preoperative risk findings such as ASA scores and patient comorbidities, and intraoperative findings such as location and diameter of perforation, and MPI, making it meaningful to compare these two techniques.

Although the MPI were the same, less physiological saline was used to wash out the abdomen in LG. We think that this

was due to targeted irrigation and aspiration thanks to the better field of view in laparoscopy. Especially in the conventional group, the pelvic area was blindly washed out and aspirated because the incision was in the upper midline. Bertleff et al. [24] state that there was no evidence that irrigation reduces intra-abdominal sepsis. In our study, the mean fluid volumes used for irrigation in two groups did not affect the development of intra-abdominal sepsis.

In the present study, the mean operating time was longer in the LG, which was consistent with many studies and meta-analyses [8, 13, 20, 25-27]. In a prospective controlled study by Siu et al. [28], the mean operation time was significantly shorter in the LG. This was one of the rare contradicting studies in the literature. We think that the longer operation time in the LG may be caused by laparoscopic peritoneal lavage, since this procedure requires different patient positions to aspirate all quadrants.

One of the advantages of laparoscopic surgery is less postoperative pain. In a study by Siow et al. [22], VAS scores were measured for 4 days, which revealed that VAS scores were significantly lower in the LG. In the LAMA study, shorter VAS scores were found in the laparoscopy group on days 1, 3 and 7. However, there was no difference between the VAS scores investigated on the 28th day [24]. In a study by Kumar et al. [25], postoperative second day VAS score was lower in the LG. In another prospective study, VAS scores were similar between the groups within the first 12 hours, and significantly lower in the LG from the 24th hour onwards [29]. In another study, no difference was found within the first 24 hours [30]. In our study, 24th hour VAS score was lower in the LG. The literature and our study revealed that significantly low VAS scores were observed in the LG at 24 hours and later.

Our patients began oral feeding significantly earlier in the LG. In previous meta-analyses and studies, significantly early oral feeding tolerance was observed in the laparoscopy group, which is consistent with our results [12, 18, 25]. In laparoscopic surgery, less gastrointestinal intervention, less postoperative pain, and early mobilization may cause patients to return to the daily activities of the gastrointestinal tract earlier [18].

Passing gas was considered an indication of postoperative bowel movements, which began earlier in the LG. In the literature, there is no study comparing the time of bowel movements to return to normal.

There were many studies reporting that the length of hospital stay is shorter in the LG [12, 13, 20, 22, 25, 27], and others reporting no significant differences [24, 31, 32]. We found significantly shorter length of hospital stay in the LG. This may be explained by earlier oral feeding, normalization of bowel movements, and less post-operative pain.

In the literature, superficial wound infection was observed less in the LG [20, 25, 32]. Similarly, we observed significantly less superficial wound infection in the LG. In the meta-analysis of Gabriel et al. [33], as in ours, pulmonary complications were less in the LG. More postoperative pain in the CG causes patients to have difficulty in breathing exercises, while restricting mobilization, and leading to increased atelectasis. Postoperative leakage, prolonged ileus, separation of fascia and intra-abdominal abscess were similar in both groups. However, total complications were significantly less in the LG. In the

literature, there was no significant difference in terms of postoperative leakage, prolonged ileus, intraabdominal abscesses between the two groups [20, 26, 27, 32, 34]. However, in studies comparing total complications, significantly less complications were observed after LG [13, 18, 22].

In the previous studies, re-operation rates were similar between the LG and CG [18, 20, 26, 35]. In present study, the rates of reoperation and the number of patients undergoing interventional drainage were similar between the two groups; however, the total number of patients requiring secondary intervention was lower in the LG.

In a meta-analysis by Zhou et al. [18], there was no difference in mortality rates between the two groups in randomized controlled trials, whereas in nonrandomized studies, mortality was significantly higher in the CG. In another meta-analysis by Tan et al. [32], mortality rates were similar in both groups. In a review by Varcus et al. [36], mortality was higher in the CG. However, in this study, CG also included patients with preoperative septic shock and high ASA score. This may have caused the high mortality rates in the conventional group. In our study, mortality rates were similar between the two groups. This may be explained by the fact that patients in septic shock were excluded and there was no difference between the ASA scores.

Limitations

This is one of the studies with the largest number of patients comparing the results of the laparoscopic and conventional Graham's omentopexy procedure. However, the retrospective nature of the study may be considered as its limitation. Prospective randomized controlled studies are needed to support the results of this article.

Conclusions

Our case series reveals that laparoscopic repair for PUP results in earlier oral feeding and bowel movements, decreased postoperative pain, superficial wound infections, pulmonary and total complications, secondary intervention, and shorter length of hospitalization when compared with conventional repair. Longer operation time was its only disadvantage. With these results, we believe that laparoscopic approach in the treatment of PUP is superior to conventional surgery and can be used safely.

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Anatomical variations of cystic artery: A digital subtraction angiography study

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Abstract

Background/Aim: Branching variations in the cystic and hepatic arteries may lead to bleeding and mortal complications during surgery. This study aimed to demonstrate the relationship between cystic artery (CA) variations and hepatic artery branching patterns among an Anatolian population using Michel's classification and compare the distribution of these variations among genders.

Methods: Angiographies performed between 2014-2017 were retrospectively evaluated and DSA images of 303 patients (84 females and 219 males) were included in this cross-sectional study. Michel's classifications of the hepatic arteries and CA variations of the patients were noted, and each was analyzed separately, along with gender-related branching differences.

Results: Hepatic arteries of 256 patients could be evaluated according to Michel's classification, the most frequent being Michel's class I (69.9 %). Thirty patients (9.9%) were excluded from CA-related statistical analyses since they had undergone a cholecystectomy. CAs were not visualized in fifty-five (18.2%) of the remaining patients. Of the 218 patients with apparent CAs, eleven females (19.3%) and twenty males (12.4%) had double cystic arteries (P=0.201). Two hundred and twelve (85.1%) CAs originated from the right hepatic artery (RHA), which was the most common parent artery. No significant relationship was found between Michel's classification and CA origin among different genders (P=0.532).

Conclusion: An overlooked anatomic variation could lead to many iatrogenic complications during diagnostic and therapeutic interventions; thus, variations of the vascular structures have attracted medical professionals' interest. This study focuses on the variations of the cystic artery and its relationship with hepatic arterial branching variations.

Keywords: Cystic artery, Michel's classification, Digital subtraction angiography, Variation

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Introduction

The celiac trunk is the first ventral branch of the abdominal aorta which usually originates at about the 12th thoracic vertebra level. It divides into left gastric, common hepatic, and splenic arteries. The common hepatic artery (CHA) then gives rise to its two terminal branches: The proper hepatic artery (PHA) and the gastroduodenal artery (GDA). Proper hepatic artery soon divides into right and left hepatic arteries. In some individuals, the right hepatic artery (RHA) arises from the superior mesenteric artery (SMA) and is named "aberrant right hepatic artery" (abRHA). The left hepatic artery (LHA) stemming from the left gastric artery (LGA) is called the aberrant left hepatic artery (abLHA). The CA typically arises from RHA and then bifurcates into superficial and deep branches to supply the gallbladder and the cystic duct. Superficial and deep branches supply peritoneal and nonperitoneal surfaces of the gallbladder, respectively. In 25% of individuals, the superficial and deep branches of the cystic artery can arise from different arterial origins. Michel called them "double cystic arteries" (Figure 1) [1-3].

Figure 1: Digital Subtraction Angiography images of double cystic artery
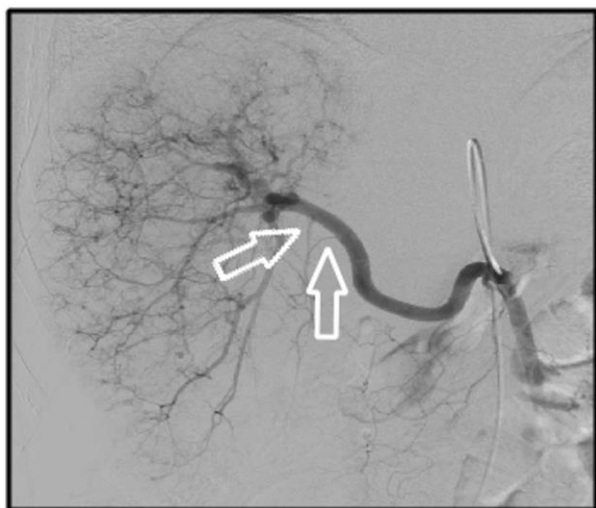
The complex vascular anatomy of the liver was presented in detail in Michel's classification. Origin of the CA and branching pattern of the hepatic arteries from the nearby vessels vary widely [4]. Variations of the CA are a critical issue for surgeons, interventional radiologists, and anatomists. These variations may have clinically important consequences.

Variations of CA and branching pattern of the hepatic arteries in a sample of an Anatolian population were analyzed and presented in this study.

Materials and methods

Patients with selective celiac and superior mesenteric angiographies were included in this retrospective study, for which approval was obtained from Ankara University Local Ethics Committee (I10-658-20). Patients with a history of hepatic resection/surgery, prior cholecystectomy, prior hepatic arterial embolization (Transarterial chemo/radioembolization) were excluded. Digital subtraction angiographic (DSA) images of 303 patients obtained between 2014-2017 were evaluated for hepatic arterial branching patterns and CA variations. The patients' ages, genders, branching types of the hepatic artery, and CA variations were recorded and statistically analyzed.

All DSA images were obtained with a dedicated device (Artis Zee Floor, Siemens, Erlangen, Germany) under local anesthesia to evaluate the vascular anatomy. The common femoral artery was punctured for catheterization and 5F catheters (Cobra or Simmons, Boston Scientific, Natick, MA, USA) were used for selective celiac and superior mesenteric angiographies. A coaxial microcatheter (Progreat, 2.7F, Terumo, Tokyo, Japan) was used whenever needed by the operator. A nonionic contrast medium (Xenetix 350 mg/ml, Guerbet, France) was injected through a power injector (Medrad, Indianola, Pennsylvania, USA) while patients were holding their breath during celiac or superior mesenteric angiographies. The injection parameters for celiac and superior mesenteric angiographies had a total contrast media volume of 15-21 ml with an injection rate of 5-7 ml/s.

Statistical analysis

The variables were presented as minimum-maximum values, mean, standard deviation, frequency, and percentage. Pearson chi-square and Fisher exact tests were used to assess categorical variables. The statistical analyses were performed with IBM SPSS (version 20). $P<0.05$ was considered statistically significant in all tests.

Results

A total of 303 patients (84 females, 219 males) were included in this study. The median age of the patients was 60.45 (11.38) years (17 – 90 years) (Table 1).

The CAs of 57 females and 161 males could be visualized, totaling 218 patients. The most frequent origin of CA was the RHA (n=212, 85.1%) (Table 2) (Figure 2). Double CAs were found in 31 (14.2%) patients, eleven (19.3%) females, and twenty (12.4%) males (Table 3). CAs of 85 patients could not be visualized either because of a previous cholecystectomy (9.9%) or technical inadequacy (18.2%). The number of CAs was similar between males and females ($P=0.201$).

Table 1: Demographic variables

Variables	Mean (SD) (Min-Max)
Age	60.45 (11.38) (17-90)
Gender	n(%)
Female	84 (27.7%)
Male	219 (72.38%)
Total	303(100%)

Table 2: Origin of cystic artery

Origin of cystic artery	n (%)
RHA	212 (85.1)
abRHA	10 (4.0)
PHA bif.	1 (0.4)
PHA	6 (2.4)
LHA	3 (1.2)
abLHA	4 (1.6)
CHA	5 (2.0)
GDA	7 (2.8)
unclassified	1 (0.4)

RHA: Right hepatic artery, abRHA: aberrant right hepatic artery, PHA bif: proper hepatic artery bifurcation, PHA: proper hepatic artery, LHA: left hepatic artery, abLHA: aberrant left hepatic artery, CHA: common hepatic artery, GDA: gastroduodenal artery

Table 3: Comparison of cystic artery number between males and females

Number of cystic arteries	Female (n%)	Male (n%)	P-value
Single	46 (80.7)	141 (87.6)	0.201
Double	11 (19.3)	20 (12.4)	

The hepatic arteries of 256 patients were categorized by Michel's classification, and Michel's class I was the most frequent branching pattern (69.9%) (Table 4) (Figure 3). Michel's classification distributions of the hepatic arteries among different genders were similar ($P=0.532$). Forty-seven (15.5%) patients' hepatic arterial branching patterns were not analyzed due to prior hepatic surgeries or because of an unclassified branching pattern

according to Michel's classification. No significant relationship was found between Michel's classification and CA origin (*P*<0.001) (Table 5).

Figure 2: CA originated from the RHA
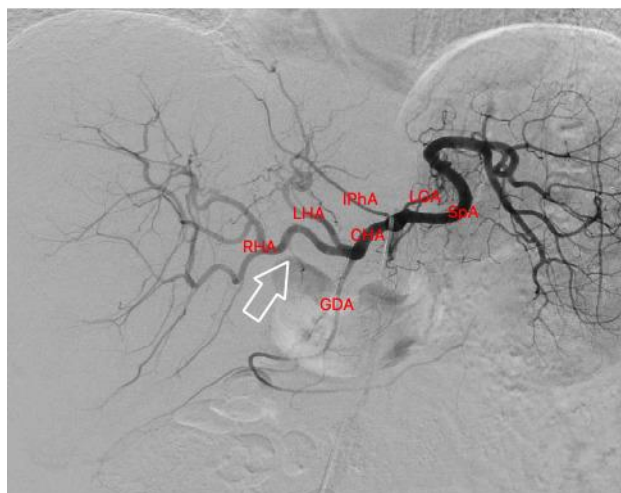
White arrow: Cystic artery (CA), Right hepatic artery (RHA), left hepatic artery (LHA), common hepatic artery (CHA), gastroduodenal artery (GDA), left gastric artery (LGA), splenic artery (SpA), inferior phrenic artery (IPhA)

Figure 3: Michel type I
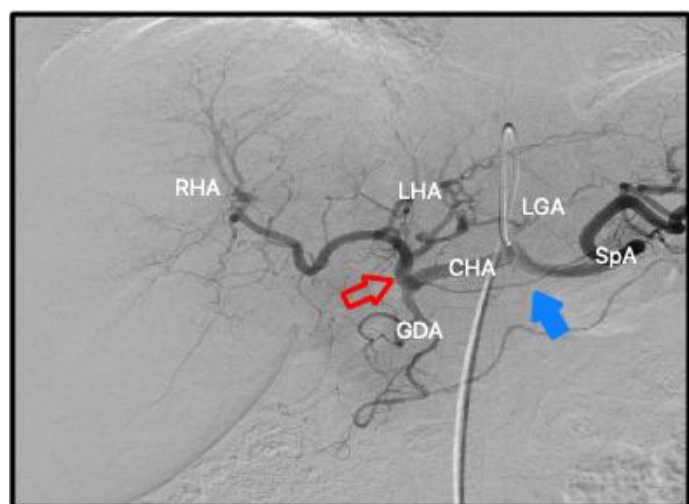
Blue arrow: Right gastric artery, Red arrow: Proper hepatic artery, Right hepatic artery (RHA), left hepatic artery (LHA), common hepatic artery (CHA), gastroduodenal artery (GDA), left gastric artery (LGA), splenic artery (SpA)

Table 4: Distribution of cases according to Michel's classification

	Female n (%)	Male n (%)	Total n (%)
I	45 (66.2)	134 (71.3)	179(69.9)
II	7 (10.3)	17 (9.0)	24 (9.4)
III	7 (10.3)	15 (8.0)	22 (8.6)
IV	2 (2.9)	3 (1.6)	5 (2)
V	4 (5.9)	13 (6.9)	17 (6.6)
VI	0	4 (2.1)	4 (1.6)
VIII	2 (2.9)	1 (0.5)	3 (1.2)
IX	1 (1.5)	1 (0.5)	2 (0.8)

Table 5: Relationship between Michel's classification and origin of cystic artery

Michel's classification	Origin of cystic artery n (%)							
	RHA	abRHA	bif PHA	PHA	LHA	abLHA	CHA	GDA
I	133 (89.9)	-	-	4 (2.7)	1 (0.7)	-	5 (3.4)	5 (3.4)
II	13 (81.2)	-	1 (6.2)	1 (6.2)	-	-	-	1 (6.2)
III	12 (60)	7 (35)	-	-	1 (5.0)	-	-	-
IV	3 (100)	-	-	-	-	-	-	-
V	13 (86.7)	-	-	-	1 (6.7)	1 (6.7)	-	-
VI	3 (75)	1 (25)	-	-	-	-	-	-
VIII	2 (100)	-	-	-	-	-	-	-
IX	2 (100)	-	-	-	-	-	-	-

RHA: Right hepatic artery, abRHA: aberrant right hepatic artery, PHA bif: proper hepatic artery bifurcation, PHA: proper hepatic artery, LHA: left hepatic artery, abLHA: aberrant left hepatic artery, CHA: common hepatic artery, GDA: gastroduodenal artery

Discussion

Variations of the vascular structures and recognition of these variations are of grave importance in diagnostic and therapeutic procedures. An unnoticed anatomic variation could lead to numerous life-threatening pitfalls during surgical or interventional treatments. Thus, vascular variations have attracted medical professionals' interest and have always been the center of interest of many specialties.

There are many studies in the literature presenting hepatic vascular or CA variations separately [4-9]. Procedures like hepatic tumor resection, transplantation, trans-arterial chemo/radioembolization require a complete detailed assessment of hepatic and cystic vessel anatomy and their variants. Many inadvertent consequences including inadequate embolization, iatrogenic tissue necrosis, or life-threatening intraoperative hemorrhage may only be prevented by proper evaluation and recognition of the anatomy of the intended vessel. Therefore, CA and hepatic arterial variations were analyzed in this study.

Uğurel et al. [10] and Du et al. [11] analyzed hepatic arterial branching and reported the most frequent branching pattern as Michel's class I with 52%, and 76.3% prevalence, respectively. In terms of Michel's classification, the results of our study are in concordance with the mentioned literature. In their review, Andall et al. evaluated the origin of CA, also stating similar results to our study in terms of the parent artery of CA [12].

Laparoscopic cholecystectomy is preferred over open surgery for the treatment of gallbladder diseases. However, bleeding is still a common complication of the procedure. Because of the narrow visual field of operation site and CA variations, intraoperative dissection of Calot's triangle requires advanced surgical experience. The Calot triangle which is bounded by the common hepatic duct, cystic duct, and the undersurface of the liver, accommodates several tiny cystic arteries [13-15]. 1.5 per 1000 laparoscopic cholecystectomy procedures were converted to open surgery because of hemorrhagic complications related to the CA injuries [12, 16, 17]. The link between Michel's classification and CA origin was evaluated in the current study. Although no significant relationship between Michel's classification and CA origin was found, Michel's 3rd group had the least rate of RHA as a parent artery of cystic artery among all Michel's groups (60%). This should be remembered when performing laparoscopic cholecystectomies to patients with RHAs originating from the superior mesenteric artery. We speculate that hemorrhagic complications occurring during laparoscopic cholecystectomies could potentially be related to double or single cystic arteries originating from an artery other than the RHA. Studies conducted with larger sample sizes will yield more accurate findings.

Mlakar et al. [8] and Kang et al. [18] reported that double CAs were observed in 14-25% of individuals among different populations. Double CA prevalence was 14.2% in our study, which was consistent with the literature. We also investigated gender-based differences in double CAs. Despite the insignificant difference, there was a slight female predominance (19.3% vs. 12.4%).

Bakheit et al. [19] and Saidi et al. [20] analyzed the position of CA with regards to the cystic, hepatic, and bile ducts. Our research was not this thorough in this regard, which may be considered a limitation. However, our study is from the view of endovascular radiology. The percutaneous endovascular approach provides a targeted treatment without damaging the neighboring structures.

There are many options to evaluate CA variations, including ultrasound imaging, computed tomography

angiography, magnetic resonance angiography, digital subtraction angiography, operative and cadaver dissections [4, 13, 18, 21-25]. In the present study, CA variations were analyzed by DSA images. Small-sized vessels in the abdominal cavity may be misinterpreted by some imaging methods because of the superposing and intermingling tissue and structures. They are also likely to be damaged in operative or cadaver dissections. DSA is the gold standard of vascular imaging and allows visualization of the branching patterns of the vascular territory. It is also useful in isolating the artery of interest from other tissues while preventing iatrogenic damage to the vessels, all of which add value to the present study.

Limitations

The retrospective nature is the most important limitation of this study. Another limitation could be the patient population which mainly consisted of patients with tumors. Since patients with prior interventions to the coeliac and superior mesenteric arterial axis were excluded from data analyses, this potential limitation has been neglected. Although the present work includes complementary data about the missing points of the previous studies in the literature, a larger number of cases are required for significant results.

Conclusions

Studies on regional differences give a preliminary idea to the clinicians and the scientific literature contains a rich archive of studies for all types of anatomical variations. An unnoticed variation could lead to many complications during therapeutic interventions, which could be prevented with the recognition of anatomic variations during diagnostic imaging. Our work serves as valuable data to further understand the cystic artery anatomy in an Anatolian population.

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Retrospective assessment of fungal pathogens isolated from various clinical samples in a tertiary care hospital in Turkey: A cross-sectional study

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Abstract

Background/Aim: Fungal infections are an emerging health problem worldwide and can be caused by a broad variety of fungal pathogens. This study aimed to retrospectively determine and evaluate the fungal pathogens isolated from various clinical samples in our laboratory.

Methods: A total of 996 clinical samples obtained from 803 patients who visited Karabuk University Training and Research Hospital microbiology laboratory between January 2019-December 2020 were included in this study. The BD-Phoenix 100 automated microbiology system was used for the identification of strains.

Results: Among 803 patients, 52.4% were female and 47.5% were male. The median age of the patients was 76 (0-99) years. Urine (49%) and blood (27.6%) samples were evaluated the most. The most common fungal pathogen was *Candida albicans* (48.7%), followed by *Candida tropicalis* (16.5%), *Candida parapsilosis* (10.6%), *Candida glabrata* (9%), *Saccharomyces cerevisiae* (5.7%), and *Trichosporon* species (3.1%). While more than 90% of fungal strains were isolated from the inpatients, 9% were isolated from the outpatients (p<0.05). Among all, 69.4% of strains were isolated from the intensive care units, followed by internal medicine (5.5%), palliative care (5%), urology (3.6%), and orthopedics and traumatology clinics (2.1%).

Conclusion: Although *C. albicans* is still the most common fungal pathogen, the incidences of non-albicans candida and other fungi are increasing worldwide. Therefore, each country should figure out its local fungal profile and update its antifungal treatment protocols accordingly.

Keywords: *Candida albicans*, *Candida tropicalis*, *Saccharomyces cerevisiae*, *Trichosporon asahii*

Introduction

Fungal infections are an emerging health problem worldwide and can be caused by a broad range of fungi. They generally occur in immunosuppressive patients, but healthy individuals can also be infected by inoculation during invasive procedures or inhalation of fungal spores [1].

More than 100,000 fungal species are found and approximately three hundred are pathogenic for humans. However, only about 10-15% of pathogenic fungi usually cause systemic mycosis [2]. The pathogenic fungi, such as Blastomyces, Coccidioides, Paracoccidioides, Histoplasma, etc., have a restricted geographic distribution and cause clinical lesions in healthy humans. The opportunistic fungi, such as *Cryptococcus neoformans*, *Candida albicans*, etc., have a ubiquitous distribution and do not provide long-term immunity; hence, relapses are noted. Especially candidiasis and candidemia responsible for many opportunistic fungal infections [3,4]. Due to immune system disorders, *Candida* species (spp.) can cause candidemia and deep tissue infection. The isolation of *Candida* spp. from the urogenital, respiratory, and digestive systems is difficult to interpret. This is due to the presence of *Candida* spp. in the normal flora of the mucosal surface [5,6].

The risk of fungal infection increases in immunocompromised patients, such as those receiving cancer treatments, solid organ transplantation, corticosteroid, or chemotherapy treatment, in case of invasive procedures (catheter, dialysis, aspiration), some viral infections, burns, traumas, and among HIV-infected patients. The most important risk factors for these groups are prolonged use of broad-spectrum antibiotics, and colonization of mucosal surfaces and catheters [6].

Fungal infections can affect various organ systems and cause various clinical syndromes such as meningitis, sinusitis, osteomyelitis, granuloma, and brain abscess [3]. Recently, the increased frequency of hospital-acquired infections caused by opportunistic fungal pathogens is one of the great concerns.

Successful fungal infection management depends on the choice of an effective antifungal drug. The success of fungal treatment is firstly based on the accurate identification of the fungal pathogen. The diagnosis and treatment of fungal infections are challenging. Direct microscopic examination, routine stains, culture, serological and molecular tests obtained from the sterile sites of the body or through demonstration of fungal tissue invasion by histopathological examination aid in the diagnosis of fungal infection [7].

This study aimed to retrospectively determine and evaluate the fungal pathogens isolated from various clinical samples in our laboratory between 2019-2020.

Materials and methods

A total of 996 clinical samples obtained from 803 patients positive for fungal pathogens in Karabuk University Training and Research Hospital between January 2019- December 2020 were included in this cross-sectional study. If the same species was grown in simultaneous samples of the same patient, only one was included.

Blood and sterile body fluids were inoculated in BD-BACTEC Plus vials (Becton-Dickinson, USA) and incubated in BACTEC FX fully automated blood culture system for seven days. Other samples were cultured on 5% sheep blood agar (BD), chocolate agar (BD), Eosin Methylene Blue agar (BD), and Sabouraud dextrose agar (BD), and then incubated at 37 °C for 24-48 hours. The strains determined as yeasts in Gram staining were identified with the BD- Phoenix^{TM} 100 (Becton Dickinson, USA) automated system.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS for IBM-PC 20.0; SPSS Inc., USA). Descriptive statistics were given as number (n), percentage (%), and median values. The Kolmogorov–Smirnov test was used to determine whether the variables were normally distributed. For the comparison of continuous variables, two-sample t-test was used. The Pearson's Chi-squared test or Fisher's Exact test was used for comparison of categorical variables if applicable. A probability (*P*) value of <0.05 was considered statistically significant at a 95% confidence interval.

Results

Among 803 patients, 52.4% (421/803) were female and 47.5% (382/803) were male. The median age of the patients was 76 (0-99) years. The distribution of the numbers and age ranges of patients are shown in Table 1.

Table 1: The number of gender and age of the patients

Age	Female	Male	Total	Mean (SD)
0-20	7	7	14	8.3 (7.1)
21-40	27	8	35	30 (5.8)
41-60	66	51	117	53.8 (5.2)
61-70	63	87	150	66.3 (2.6)
> 71	258	229	487	80.7 (6.2)
Total	421	382	803	70.6 (16.6)

SD: Standard deviation

The most common fungal pathogen was *Candida albicans* with 48.7% (485/996). *Candida tropicalis* was detected in 16.5% (164/996), *Candida parapsilosis*, in 10.6% (106/996), *Candida glabrata, in* 9% (90/996), and *Saccharomyces cerevisiae, in* 5.7% (57/996). *Candida lusitania*, *Trichosporon. asahii*, *Candida kefyr*, *Candida krusei* and *Trichosporon mucoides* were detected in 3.3%, 3%, 2.2%, 0.8%, 0.1%, retrospectively. The distribution of the isolated fungal pathogens is shown in Figure 1.

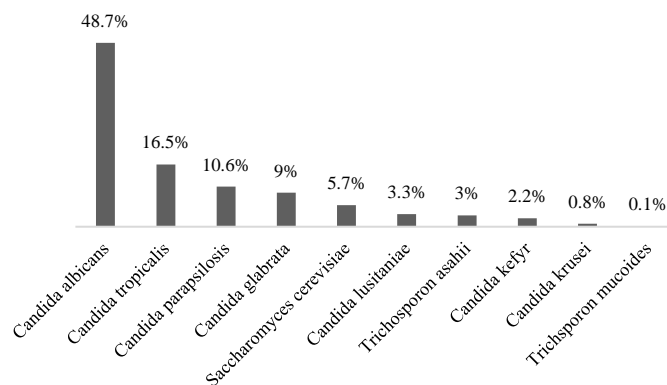Figure 1: The distribution of the isolated fungal pathogens

Table 2: The distribution of the samples according to the isolated fungal pathogens

Sample	Candida albicans n (%)	Candida. tropicalis n (%)	Candida parapsilosis n (%)	Candida glabrata n (%)	Saccharomyces cerevisiae n (%)	Candida lusitaniae n (%)	Trichosporon asahii n (%)	Candida kefyr n (%)	Candida krusei n (%)	Trichosporon mucoides n (%)	Total n (%)
Urine	235 (48.5)	75 (45.7)	18 (17)	43 (47.8)	50 (87.7)	20 (60.6)	30 (100)	14 (63.6)	3 (37.5)	-	488 (49)
Blood	111 (22.9)	63 (38.4)	63 (59.4)	28 (31.1)	1 (1.8)	7 (21.2)	-	1 (4.5)	1 (12.5)	-	276 (27.6)
ETA	77 (15.9)	7 (4.3)	8 (7.5)	10 (11.1)	5 (8.8)	4 (12.1)	-	5 (22.7)	2 (25)	-	118 (11.8)
Wound	9 (1.9)	10 (6.1)	2 (1.9)	7 (7.8)	-	-	-	1 (4.5)	-	-	29 (2.9)
Sputum	21 (4.3)	2 (1.2)	-	1 (1.1)	1 (1.8)	-	-	-	-	1 (100)	26 (2.6)
External Ear	5(1)	1 (0.6)	6 (5.7)	-	-	-	-	-	2(25)	-	18 (1.8)
Vagina	16 (3.3)	1 (0.6)	-	-	-	-	-	-	-	-	17 (1.7)
Catheter	3 (0.6)	4 (2.4)	3 (2.8)	1 (1.1)	-	1 (3)	-	-	-	-	12 (1.2)
BAL	8 (1.6)	-	1 (0.9)	-	-	1 (3)	-	1 (4.5)	-	-	11 (1.1)
Pleural Fluid	-	-	1 (0.9)	-	-	-	-	-	-	-	1 (0.1)
Total	485 (48.7)	164 (16.5)	106 (10.6)	90 (9)	57 (5.7)	33 (3.3)	30 (3)	22 (2.2)	8 (0.8)	1 (0.1)	996 (100)

Table 3: The distribution of isolated fungal pathogens according to clinics

Clinics	Candida albicans n (%)	Candida glabrata n (%)	Candida kefyr n (%)	Candida krusei n (%)	Candida lusitaniae n (%)	Candida parapsilosis n (%)	Candida tropicalis n (%)	Saccharomyces erevisiae n (%)	Trichosporon asahii n (%)	Trichsporon mucoides n (%)	Total n (%)
Intensive Care Units	328 (67.6)	50 (55.5)	16 (72.8)	4 (50)	30 (91)	76 (71.7)	128 (78)	39 (68.5)	19 (63.4)	1 (100)	691(69.4)
Internal Medicine	26 (5.3)	10 (11.2)	1 (4.5)	-	-	2 (1.9)	13 (8)	6 (10.5)	1 (3.3)	-	59 (5.9)
Palliative Care	28 (5.8)	1 (1.1)	-	-	2 (6)	9 (8.5)	7 (4.3)	5 (8.8)	2 (6.7)	-	54 (5.4)
Urology	18 (3.8)	6 (6.7)	1 (4.5)	1 (12.5)	-	3 (2.8)	2 (1.2)	1 (1.7)	5 (16.7)	-	36 (3.6)
Orthopedics and Traumatology	8 (1.6)	6 (6.7)	-	-	-	3 (2.8)	4 (2.5)	-	-	-	21 (2.1)
Chest Diseases	13 (2.7)	1 (1.1)	3 (13.7)	-	-	1 (0.9)	-	-	-	-	19 (1.9)
Otorhinolaryngology	6 (1.2)	-	-	2 (25)	-	10 (9.5)	1 (0.6)	-	-	-	19 (1.9)
Gynecology and Obstetrics	19 (3.9)	1 (1.1)	-	1 (12.5)	-	-	-	-	-	-	21 (2.1)
Nephrology	8 (1.6)	1 (11.1)	1 (4.5)	-	-	2 (1.9)	5 (3)	-	-	-	17 (1.7)
Oncology	4 (0.8)	6 (6.7)	-	-	-	-	-	-	-	-	10 (1)
Infectious Diseases	5 (1)	2 (2.2)	-	-	-	-	-	3 (5.3)	-	-	10 (1)
Pediatric Diseases	5 (1.1)	1 (1.1)	-	-	1 (3)	-	2 (1.2)	-	-	-	9 (0.9)
Emergency	6 (1.2)	1 (1.1)	-	-	-	-	-	-	-	-	7 (0.7)
Cardiology	3 (0.6)	1 (1.1)	-	-	-	-	1 (0.6)	2 (3.5)	2 (6.7)	-	9 (0.9)
Neurology	6 (1.2)	-	-	-	-	-	1 (0.6)	1 (1.7)	1 (3.3)	-	9 (0.9)
General surgery	1 (0.2)	2 (2.2)	-	-	-	-	-	-	-	-	3 (0.3)
Gastroenterology	1 (0.2)	-	-	-	-	-	-	-	-	-	1 (0.1)
Dermatology	0	1 (1.1)	-	-	-	-	-	-	-	-	1 (0.1)
Total	485	90	22	8	33	106	164	57	30	1	996(100)

The most common samples were urine (49%), and blood (27.6%), followed by endotracheal aspirate (ETA) (11.8%), and wound (2.9%). The other samples were sputum, external ear swab, vaginal swab, bronchoalveolar lavage fluid (BAL), and pleural fluid with 2.6%, 1.8%, 1.7%, 1.1%, and 0.1% respectively. Fungal pathogens were also isolated from catheters (1.2%). The distribution of the samples according to the isolated fungal pathogens is shown in Table 2. While 90.8% (n=729) of the strains were isolated from in-ward or intensive care patients, 9.2% (n=74) were isolated from outpatients. The distribution of the fungal pathogens was examined according to clinics, and there was a significant difference between outpatients and inpatients ($P<0.05$).

Fungal strain positivity was evaluated according to where the samples were received. Most positive samples were sent from the intensive care units (69.4%), followed by internal medicine, palliative care, urology, and orthopedics, and traumatology (5.5%, 5%, 3.6%, 2.1%, respectively). The distribution of isolated fungal pathogens according to the clinics is shown in Table 3.

Discussion

Fungal infections cause severe health concerns worldwide. Globally, more than a billion people are directly affected by mycoses, 150 million of which were exposed to life-threatening infections [8]. Candida spp. cause nosocomial infections, especially in critically ill patients admitted to the intensive care units. The mortality rate is between 15-35% depending on the *Candida* species [9]. Candida is a member of the skin flora, mucosa, and gastrointestinal system [9,10]. Mucosal colonization begins right away after birth, which is associated with an increased risk for endogenous infection. Candidemia is the most common systemic mycosis, and its incidence has gradually increased in the last two decades. Moreover, it has been reported as the fourth most common cause of nosocomial bloodstream infections [11]. This is associated with immune suppression, extensive use of invasive procedures, and intensive antibiotic treatment. In this study, *C. albicans* was the most isolated fungal pathogen from blood samples, with a rate of 40.2% (111/276). *C. tropicalis* and *C. parapsilosis* were each detected in 22.8% (63/276) and *C. glabrata* was detected in 10.2%. Similarly, *C. albicans* has been reported as the main fungal pathogen in blood samples in Turkey, with a rate ranging from 40% -57% [12-16]. Additionally, *C. tropicalis* and *C. parapsilosis* were reported as the 2nd and 3rd most common, respectively [13,16]. In 2571 blood samples isolated in France between 2002-2010, *C. albicans* constituted 56%, *C. glabrata*, 18.6%, *C. parapsilosis*, 11.5%, and *C. tropicalis*, 9.3% of bloodstream infections [17]. In a study conducted in China, the most common fungal pathogens isolated from blood cultures between 2007 and 2018 were *C. albicans, C. tropicalis, C. glabrata,* and *C. parapsilosis,* with rates of 43%, 18%, 12%, and 9%, respectively. It also was noted that the

prevalence of *C. albicans* decreased, while other *Candida* species were increased each year [18].

Falagas et al. have noticed that *C. albicans* is the predominant species worldwide, and its incidence was reported to range from 17% - 87% [19]. While the *C. albicans* incidence was highest in North and Central Europe and the US, non-albicans *Candida* spp. were more frequent in Asia, South America, and Southern Europe. Globally, the incidence of *C. albicans* decreased over time, while a rise in *C. tropicalis* and *C parapsilosis* infections were observed. *C. glabrata* and *C. krusei* infections remained stable [18,19]. The rising number of non-albicans *Candida* spp. such as *C. parapsilosis, C. glabrata, C. krusei, C. tropicalis* is worrisome. These species are primarily intrinsic and acquired resistance to azoles and echinocandins, agents used in the prophylaxis and treatment of *Candida* infections [11,19,20].

In this study, we isolated fungal pathogens mostly from urine samples. Fungal urinary infections have recently increased because of invasive surgical and medical procedures. Diabetes Mellitus, urinary tract anomalies, prolonged antibiotic use, and urinary catheterization are the main risk factors [21]. Renal candidiasis generally develops due to hematogenous spread in 80% of patients with candidiasis. Lower urinary infection often occurs due to dissemination from a catheter or the genital/gastrointestinal tract [21,22]. Most candiduria cases are asymptomatic. The presence of yeasts with leukocytes in the urine of symptomatic patients indicates an upper urinary tract infection [23] Although bacterial species are the main causes of urinary infections, fungal pathogens are the causative agents in 10%. Since *Candida* spp. can also be found in the genitourinary flora, it is challenging to decide whether there is contamination or colonization/infection in urine cultures. Cases of recurrent fungal growth should be evaluated with clinical findings [22-24].

In the present study, *C. albicans* was isolated from urine samples at a rate of 51% (235/488), followed by *C. tropicalis* (15.4%), *S. cerevisiae* (10.3%), *C. glabrata* (8.8%), *T. asahii* (6.2%) and *C. lusitania* (4.1%). Similarly, Karalti et al. isolated 54.2% *C. albicans* and 14.1% *C. tropicalis* from urine samples [24]. On the other hand, Atalay et al. mostly detected *C. albicans* and *C. glabrata* in urine samples at a rate of 30% [23]. It is noteworthy that *S. cerevisiae* is the third most common species in urine. We also isolated it from one blood sample and one ETA sample. Saccharomyces species is a ubiquitous colonizer of human mucosal surfaces. Saccharomyces spp. can colonize the urinary tract system in the setting of chronic disease, but these yeasts have rarely been determined to cause renal diseases such as a renal abscess or pyelonephritis [25]. Senneville et al. reported a case of *S. cerevisiae* fungus balls that were associated with total bilateral ureteral obstruction in a patient [26]. This yeast species is widely used in the food industry. However, it has been reported that it causes invasive infections in some patients who are given probiotics for diarrhea due to antibiotic use. Saccharomyces infections remain rare among invasive fungal infections, although the incidence has significantly increased since the 1990s [27]. Recently, Ventoulos et al. reported bloodstream infection by *Saccharomyces* in two patients hospitalized in the intensive care units, due to SARS CoV-2 infection, after *Saccharomyces* supplementation [28]. Also, *S. cerevisiae* can cause a wide range of human infections, such as pneumonia, liver abscess,

esophagitis, peritonitis, cellulitis, urinary tract infection, and fungemia [29]. Therefore, *Saccharomyces* spp. must be considered an emerging fungal pathogen.

It is also remarkable that we isolated *Trichosporon* species at a rate of 6.2% in urine samples. *Trichosporon* spp. are basidiomycetous yeasts common in nature, also a part of the flora of the skin, respiratory and gastrointestinal tract [30]. They are causes of fatal infections in immunosuppressive patients, especially those with hematological cancers. *Trichosporon* infections have dramatically increased in recent years [31]. Urinary tract infections due to *T. asahii*, associated with indwelling medical devices, have been reported for years. Trichosporonosis has also been reported in immunocompetent patients with underlying peritoneal dialysis catheters, prosthetic valves, and urinary and intravenous catheters [32].

We isolated *C. albicans* in 67.9 % of respiratory samples. Non-*albicans Candida* species (*C. glabrata*, *C parapsilosis C. kefyr*, *C. tropicalis*, *C. krusei,* and *C. lusitaniae*) constituted 27.6% of other fungal strains, while other fungi (*S. cerevisiae* and *T. asahii)* made up 4.4%. Similarly, Sav et al. reported the most common fungal pathogen as *C. albicans* a rate of 76.8% among 849 fungal respiratory strains. The non-*albicans* frequency was 14.7% [33]. Candida spp. colonization is more common among critically ill patients. Candida airway colonization may facilitate bacterial colonization and subsequent development of bacterial pneumonia [34]. Respiratory Candida colonization in patients with ventilator-associated pneumonia was associated with longer mechanical ventilation duration and intensive care stay and higher 28-day mortality [35]. In other words, airway Candida colonization is a sign of poor prognosis.

Limitations

This is a retrospective single-center study based on laboratory data; therefore, the data of the clinical findings and treatments of patients are not available. In addition, antifungal susceptibility test results could not be included in the study, because the automated identification system does not have an antifungal test panel in our hospital. The prevalence of fungal pathogens belongs to a tertiary care hospital in the Western Black Sea region of Turkey, so the results may not reflect the general population of Turkey.

Conclusion

The profile of fungal pathogens that cause infections varies worldwide. In our study, although *C. albicans* was the predominant pathogen, the incidence of non-albicans Candida is worrying. Moreover, *Saccharomyces* spp. and *Trichosporon* spp. have emerged as causative agents in fungal infections. Therefore, the regional fungal pathogen profile should be determined and considered in the choice of empirical antifungal therapy.

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Evaluation of clinical findings and treatment options of Sydenham chorea patients

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Abstract

Background/Aim: Sydenham chorea is an autoimmune neurological disorder of the childhood which occurs due to cross-reaction of antibodies against group A beta-hemolytic streptococci in the basal ganglia. We evaluated patients with Sydenham's chorea, treatment options, recovery duration, and relapses to determine whether there is any relationship between biochemical parameters such as erythrocyte sedimentation rate (ESR), serum Anti Streptolysin Antibody (ASA), and patients' clinical course.

Methods: This case series includes patients with Sydenham chorea who visited the pediatric neurology outpatient clinics between May 2013 and September 2018. Neurologic examination was performed by a pediatric neurologist, and electrocardiography and echocardiography were performed by a pediatric cardiologist. ESR and ASA levels, treatment options, and clinical course of the disease were evaluated.

Results: Sixteen patients, with nine females (56.3%) and seven males (43.7%) were included in this study. The most seen chorea type was hemichorea. The median ASA and ESR values of the patients were 619 IU/ml (278.25-794.75) and 17.5 mm/h (7.25-27), respectively. Their median age and time until recurrence were 12 (9-14.25) years and 16 months (9-18), respectively. The median recovery period was 5.5 months (3-6). Diazepam and haloperidol were the most used secondary treatment options. Mitral insufficiency (MI) was the most frequent finding (56.3%). Benzathine penicillin and secondary prophylaxis, e.g., haloperidol, diazepam were our treatment agents of choice. ASA levels were lower among patients treated with steroids (U=9, z=-2.38, P=0.017). Age was moderately positively correlated with recovery period (age r (14) = 0.738, P=0.001), while no correlation was found between age and ESR, or recurrence period (P=0.98, P=0.33, respectively). The recovery period of generalized chorea was longer than that of hemichorea (U=10.5, z=-1.96, P=0.05). Recurrence was not related to ASA levels, ESR levels, age, or recovery period (P=0.73, P=0.89, P=0.78, P=0.83 respectively).

Conclusion: High ASA levels may not indicate steroid need, and the recovery period increases with age and in cases of generalized chorea. Instead of benzathine penicillin or other known secondary prophylactic agents, azithromycin and levetiracetam can be used in hypersensitive patients.

Keywords: Sydenham chorea, Treatment, Levetiracetam, Azithromycin

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Introduction

Sydenham chorea is a central nervous system disease characterized by sudden, involuntary, non-rhythmic aimless movement, and rapid movements involving the extremities and the face. Choreiform movements disappear during sleep and rest [1, 2]. Sydenham chorea is the most common cause of acquired chorea in children and the most prominent and late finding of acute rheumatic fever [3]. It occurs because of the cross-reaction of antibodies against group A beta-hemolytic streptococci in the basal ganglia. It often presents between the ages of 5-15 years [3].

In addition to benzathine penicillin, drugs that inhibit dopaminergic hyperactivity, such as haloperidol, pimozide, and risperidone, and drugs that act on GABA, such as benzodiazepine and valproic acid are used for treatment [3]. Immunomodulatory therapies such as corticosteroids, intravenous immunoglobulins (IVIG), and plasma exchange shorten the course of the disease and reduce complications [4]. In this case series, we retrospectively evaluated patients with Sydenham's chorea, treatment options, recovery duration, and relapses, and aimed to determine whether there is a relationship between biochemical parameters such as erythrocyte sedimentation rate (ESR), serum Anti Streptolysin Antibody (ASA) and patients' clinical courses.

Materials and methods

Sixteen patients who had visited the pediatric neurology and cardiology outpatient clinics between May 2013 and September 2018 with the diagnosis of Sydenham chorea were included in this study. Patients were evaluated retrospectively. Diagnosis of acute rheumatic fever was made according to the updated Jones criteria [5].

All patients underwent detailed physical and neurological examinations. Patients' demographic characteristics, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) values, serum Anti Streptolysin Antibody (ASA), cerebral magnetic resonance imaging (MRI) reports were evaluated. ASA titers >200 IU/ml, ESH >20 mm/h, CRP >5 mg/dl were considered above the normal range.

Cardiovascular system evaluations including physical examination, electrocardiography, and echocardiography were performed by a pediatric cardiologist. Examination findings, chorea type, treatments, chorea recovery time, indications for immunomodulatory treatment, resistance to treatment, and follow-up data were retrospectively investigated. Chorea was classified into hemichorea (involving one part of the body) and generalized chorea (involving all body parts). The patients were called for a monthly check-up every 15 days until chorea improved. Symptomatic treatment of the patients continued for 2-4 months after recovery. When the symptomatic treatment was discontinued, patients were called for monthly control visits, and then at three- and six-month intervals. Cardiac controls were planned according to the severity of heart involvement.

Statistical analysis

Statistical analyses were performed using SPSS 15.0 (SPSS for Windows, Version 15.0. Chicago, SPSS Inc.) program. Normally distributed variables were presented as mean (standard deviation), and non-normally distributed variables were presented as median (minimum-maximum). In the comparison between the independent groups, t-test was used for the parametric data and Mann-Whitney U test was used for the non-parametric data. The difference between the categorical data was evaluated by Chi-square and Fisher's exact tests. P-value <0.05 was considered statistically significant.

Results

A total of 16 patients, comprising 9 females (56.3%) and 7 males (43.7%), were included in this study. The median age of the patients was 12 (9-14.25) years. The demographic features are summarized in Table 1. The highest, lowest, and median ASA levels were 1330 U/ml, 96 U/ml, and 619 (278.25-794.75) U/ml. The patient who had an ESR of 39 mm/h also had elevated CRP (6.2 mg /dl). The CRP values of the rest of the patients were within normal limits. Echocardiography of the same patient showed mild mitral valve insufficiency compatible with carditis.

Table 1: Demographic features

Features	
Total	16
Gender	Female 9(56.3%)
	Male 7 (43.8%)
Median Age	12(9-14.25)
ASA	619(278.25-27)
ESR	17.5(7.25-27)
Chorea	Hemichorea 68.8%
	Generalized 31.2%
Cardiac involvement	12 patients 75%
	MI 56.3 %
First Treatment Choice	Diazepam+Haloperidol 56.3%
Recovery period	5.5 months (3-6)
Recurrence	3 patients (18.8%)

Chorea was generalized in 5 (31.2%) of patients and presented as hemichorea in 11 patients (68.8%). At the time of admission, 4 (25%) patients had right hemichorea, 7 (43.8%) patients had left hemichorea, and 1 patient had generalized chorea. Four patients with hemichorea developed generalized chorea later. Recurrence was seen in 2 of 3 generalized chorea patients. All clinical characteristics are presented in Table 2.

Table 2: Clinical characteristics of the patients

Patient	Gender	Age	ASA	ESR	Recovery time Months	Relapse Months	Chorea	Drugs used	Steroid	Heart involvement
1	F	12	303	28	6	-	Right, then Generalized	Diazepam, Valproic acid	+	MI
2	F	15	870	27	6	16	Left	Haloperidol ,Diazepam	-	MI
3	F	9	606	18	6	-	Generalized	Haloperidol,	+	MI
4	F	9	382	6	4	-	Left	Haloperidol, Diazepam	-	MI
5	F	15	111	15	9	-	Right then Generalized	Valproic acid then Haloperidol, Diazepam	+	MI,AV Block
6	M	9	1330	4	2	-	Right	Haloperidol, Diazepam	-	2^0MI
7	M	10	797	11	5	-	Left	Haloperidol, Diazepam	-	2^0MI
8	F	12	632	6	6	-	Right	Haloperidol	-	Normal
9	M	15	360	27	10	-	Left then Generalized	Haloperidol, Diazepam,	+	Normal
10	M	15	683	15	7	-	Left	Haloperidol	-	MI,TI
11	F	12	738	39	4	-	Left then Generalized	Haloperidol	+	Acute Carditis
12	F	12	237	38	3	-	Left	Haloperidol, Diazepam	-	Normal
13	M	11	96	5	6	18	Left	Levetiracetam.	+	MI
14	M	7	788	20	2	9	Right	Haloperidol, Diazepam	-	Normal
15	F	6	>800	25	2	-	Left	Haloperidol, Diazepam	-	2^0 MI
16	M	12	270	17	3	-	Right	Haloperidol, Diazepam	+	MI

AV: Atrioventricular Block, MI: Mitral insufficiency, TI: Tricuspid Insufficiency

All generalized chorea patients and 2 (18.2%) of the hemichorea patients were treated with methylprednisolone. Five patients with generalized chorea findings were admitted to the hospital and administered 1 g daily methylprednisolone for three days, followed by oral prednisolone tapered within one month. Three patients had recurrence. Methylprednisolone was not

considered in one of these patients with recurrence, whose findings responded to haloperidol. In one of the 2 patients with recurrent generalized chorea, complaints were observed 16 months after the end of the treatment. The third patient with recurrence had a history of anaphylaxis to benzathine penicillin G. Allergic rash developed with erythromycin and clarithromycin, and chorea symptoms could not be controlled with haloperidol or valproic acid. This patient was admitted to the pediatric neurology clinic due to increased involuntary movements and difficulty in self-care skills 18 months after recovery. Recurrence findings were consistent with generalized chorea and levetiracetam was administered. Because of the history of anaphylaxis to benzathine penicillin, azithromycin 500 mg tablets were used for secondary prophylaxis every 10 days.

In all patients, first haloperidol, a dopamine receptor antagonist, then diazepam, a benzodiazepine, were used to control movement disorders. The combination of diazepam and haloperidol was used in 9 patients (56.3%), only haloperidol was used in 4 patients (25%), diazepam and valproic acid combination were used in 1 patient (6.3%), diazepam, valproic acid and haloperidol combination were used in 1 patient (6.3%), and levetiracetam was administered to 1 patient (6.3%). Clinical recovery was the marker for the duration of chorea treatment. The recovery period of generalized chorea was longer than that of hemichorea (U=10.5, z=-1.96, P=0.05). Drugs were discontinued within 2 months after symptoms were controlled. Benzathine G penicillin was used for secondary prophylaxis. The median recovery period was 5.5 months (3-6). Recurrence of the chorea was seen in 3 (18.8%) patients, two (12.5%) of which were males. ASA was high in two and ESR was above 20 mm/h in one patient with recurrence.

Upon cardiac examination, 12 patients (75%) were found to have carditis. One of them was prescribed aspirin because of acute rheumatic carditis signs. Four patients had isolated chorea without heart involvement. Compared to males, insignificantly more females had cardiac involvement (P=0.77). MI was the most frequent finding in chorea (56.3%). Elevated ESR and cardiac involvement were not correlated (P=0.52). Brain MRI was performed in all patients and yielded normal results in all. There was a moderate positive correlation between age and recovery period (age r(14)=0.738, P=0.001)), while age, ESR, and recurrence period (P=0.98, P=0.33 respectively) were not correlated. Recurrence was not related to ASA levels, ESR levels, age, or recovery period (P=0.73, P=0.89, P=0.78, P=0.83 respectively.

Discussion

Sydenham chorea can be seen alone or in combination with other symptoms of acute rheumatic fever. While it usually starts unilaterally, bilateral choreiform movements may also be observed. It mostly presents as generalized chorea, and less often as hemichorea. The handwriting of the patients is impaired because they cannot perform tasks requiring fine motor skills due to choreiform movements in the hands. Speech impairment may be observed [2, 6, 7]. Motor motion instability is particularly noticeable during protrusion of the tongue and ocular fixation. Sydenham chorea is included in the major criteria for acute rheumatic fever according to the 1992 modified Jones criteria and sufficient for diagnosis [8]. Among all our patients, one presented with generalized chorea. Generalized chorea developed later during the disease in four patients who presented with hemichorea. This was attributed to incompliance with symptomatic treatment. Although very rare, the patient may become bedridden (chorea paralytic). Sydenham chorea is observed in 40-80% of patients with carditis, and 10-30% with arthritis. In 20-70%, it is the only symptom [9]. In our study, only one patient had acute carditis, and 12 patients had carditis compatible with rheumatic heart disease. The findings were consistent with isolated chorea in four patients. None of the patients had arthritis at the time of diagnosis.

Sydenham chorea and acute rheumatic fever are seen at similar ages, between 5-15 years, often around 9 years of age, and mostly in females [3, 6, 7]. In this study, the median age of chorea patients was 12 years (9-14.25) and most were females (56.3%). The youngest patient was a 6-year-old female.

It occurs 1 to 6 months after tonsillopharyngitis / pharyngitis caused by GABHS. Our patients did not have any upper respiratory tract infection at the time of diagnosis. One 6-year-old female patient had had an upper respiratory infection twice in the last 6 months. A 12-year-old female who presented with an acute carditis attack had received benzathine penicillin G treatment for tonsillitis and was diagnosed with chorea and acute carditis 1 month later.

Chorea symptoms mostly last between 8-15 weeks, while they can continue anywhere from 1 week to 2 years. Relapse may be observed in completely healed patients for up to 2 years [2, 6, 7]. The median recovery time of our patients was 5.5 months, and the latest improvement was observed 10 months later. Three (18.8%) patients had relapsed at 9 months, 16 months, and 18 months, respectively, after treatment. The patient presenting with relapse 9 months after the initial diagnosis had discontinued haloperidol 3 months before recurrence symptoms. He presented with hemichorea on the same side. The patient was started on haloperidol again and symptoms were controlled.

SC is the result of secondary immune reactivity against the basal ganglia and the brain [1, 2, 6, 10]. Antibody-related D2R signals, especially in dopaminergic neurons, lead to changes in central dopamine pathways and impaired movement [10].

While the amounts of GABA and acetylcholine in the basal ganglia are reduced, dopaminergic activity is increased, which also explains the mechanisms of action of haloperidol, valproic acid, and carbamazepine [2, 11]. Therefore, antiepileptics (valproic acid, carbamazepine) or dopamine receptor blockers (haloperidol, pimozide, risperidone) may be used in the symptomatic treatment of chorea [12, 13]. In this article, dopamine receptor antagonists were used as the first choice, and benzodiazepine was used as an add-on treatment to haloperidol to control movement disorders. Levetiracetam was started in one of the patients who did not benefit from haloperidol and valproic acid treatment. Although the mechanism of action of levetiracetam is not fully known, it has little affinity to GABA and glutamate receptors and is effective in preventing negative modulation against GABA receptors without direct binding [14]. In light of this information, it may be said that levetiracetam could lead to an increase in the efficacy of GABA. Levetiracetam reduces the synchronization of neurons in epilepsy patients and has been reported to improve movement disturbance in some movement

disorders such as essential tremor, cerebellar tremor, myoclonus, and dyskinesias caused by L-dopa [15]. Vlas et al. [16] used levetiracetam to successfully control choreoathetosis in two patients with dyskinetic CP. Şahin S et al. [17] used haloperidol in a patient diagnosed with chorea and added levetiracetam when it was ineffective, after which improvement was observed.

Because Sydenham chorea is an immune-mediated disease, corticosteroids, intravenous immunoglobulin, and plasmapheresis were shown to have benefits in selected cases. They shorten the disease course and reduce complications [9,18,19,20]. Immunosuppressive therapy is used in severe, resistant cases, in patients with side effects to symptomatic therapy, or in those who do not respond to symptomatic therapy [21]. Among our cases, methylprednisolone treatment was started in 7 (43.8%) patients. All but one of the patients receiving methylprednisolone had high ASA titers, and 3 had high ESR values.

The primary treatment of Sydenham chorea is penicillin and bed rest [22]. Penicillin prophylaxis is given for cardiac protection and does not affect relapse [2]. Azithromycin may be used in the acute period of streptococcal infections, and in some studies, the superiority of amoxicillin-clavulanate has been reported [23], although it is not recommended for secondary prophylaxis in acute rheumatic carditis [24]. We used azithromycin for secondary prophylaxis in our patient who developed a severe allergic reaction to benzathine penicillin G and an allergic rash because of erythromycin and clarithromycin. Azithromycin was used every ten days a month. No recurrence of streptococcal infection was observed with azithromycin prophylaxis. There was no deterioration in rheumatic heart disease in cardiologic controls.

Sydenham chorea symptoms improve by 6 months in most patients. Three of our patients had recurrence, one of which was female. She did not use the penicillin prophylaxis properly. The other patient had an allergic reaction to benzathine penicillin, erythromycin, and clarithromycin, and had insufficient secondary prophylaxis. Both patients with recurrence were noncompliant with secondary prophylaxis. One of these patients had a high ASA value. Recurrences most commonly occur in 1-2 years after the onset of the disease. Recurrence is defined as a new finding of chorea that lasts for at least 24 hours, occurring at least 2 months after the first attack. Recurrence is related to incompliance with prophylactic treatment, re-exposure to streptococcal infection, and no remission within the first 6 months [3, 25]. Regular penicillin prophylaxis reduces the risk of recurrence [14].

None of the patients had persistent chorea, which is characterized by symptoms lasting for more than a year [26, 27]. In the study of Gürkaş et al. [25], there were four persistent chorea patients, among which 3 had recurrence. In these patients, valproic acid was added when haloperidol was ineffective in secondary prophylaxis. According to Tumas et al. [26], persistent chorea occurs because of the molecular changes caused by haloperidol in the basal ganglia.

Treatment strategies in SC are mostly based on the physician's clinical decision-making. According to Dean and Singer, data on symptomatic therapy are based on case report presentations; therefore, individually made decisions by the practitioner are important [19].

Limitations

The limitations of this study include its retrospective and single-center design, and few numbers of patients. Instead of case reports, further studies may be planned to figure out the treatment strategies and risk factors for recurrent and persistent Sydenham's chorea.

Conclusions

Sydenham Chorea is one of the major signs of acute rheumatic fever. There is a risk of recurrence in patients using insufficient secondary prophylaxis. It may become generalized in patients presenting with hemichorea and not receiving adequate symptomatic treatment. Reaction to antiepileptics and dopamine antagonist drugs is extremely rare and makes it difficult to control symptoms. In these cases, levetiracetam may be a useful choice. Despite advances in medicine, Sydenham chorea treatment is not evidence-based. Treatment should be tailored to the clinical findings of each patient.

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Two natural materials found to reduce adhesion formation in a rat uterine horn model

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Abstract

Background/Aim: Post-operative pelvic adhesions cause various problems in patients, pose surgical difficulties to clinicians, and an increase in health costs. We compared the effectiveness of two natural materials, Trehalose (TRZ), Human Amnion Fluid (HAF), with oxidized regenerated cellulose (ORC) in terms of adhesion prevention after gynecological operations.

Methods: In this controlled experimental study, twenty-four female Wistar Hannover rats were divided into four groups: Control, TRZ, HAF, and ORC. The control group received medication used for the surgical procedure only. 3% TRZ, cell-free HAF, and 1 cm^2 ORC (interceed®) were laid on the tissue on the antimesenteric side of each uterine horn damaged with a 10-Watt bipolar cautery. Adhesions were scored 30 days after the first surgical procedure.

Results: The extent, severity, degree, total adhesion, inflammation, and fibrosis scores of the control group were significantly higher than those of the TRZ and HAF groups ($P<0.05$ for each). There was no significant difference between the Control and ORC groups in terms of inflammation ($P=0.055$), but all other parameters were significantly higher in the control group compared to the ORC group ($P<0.05$). The TRZ group had lower total adhesion scores ($P=0.019$) and histopathological scores ($P=0.015$, $P=0.001$) than the ORC group.

Conclusions: TRZ and HAF may be useful in preventing pelvic adhesions.

Keywords: Adhesions, Human amnion fluid, Interceed, Oxidised regenerated cellulose, Trehalose

Introduction

Postoperative adhesion is a common complication after abdominal surgery with an incidence of 60-90% [1]. It is known that post-operative peritoneal adhesions occur in 90% of patients who undergo gynecological surgery. In gynecology, postoperative intra-abdominal adhesions may cause infertility, organ damage due to adhesions, intestinal obstruction, and chronic pelvic pain in subsequent operations [1, 2]. It is associated with mortality ranging from 3-30% in severe adhesions [3].

The abdominal peritoneal cavity consists of two sections, visceral and parietal, which are covered with a single layer of mesothelial cells [4]. The mesothelium is very fragile and can be easily damaged due to various reasons (cutting, cauterization, ischemia, desiccation, or abrasion) [5, 6]. After surgery or injury, reperitonealization starts within 8 to 24 hours and ends in 7-10 days. Therefore, the optimal agent should be effective for at least 1 week to prevent adhesions [6-8].

Many agents have been tried to reduce adhesions. Steroidal and non-steroidal anti-inflammatory medications are used to reduce inflammation, recombinant tissue plasminogen activator [t-PA], anti-coagulants, commercial or natural barriers (absorbable material/solution/gel, liquid paraffin, human amniotic membrane) and vitamins are used to reduce fibrin formation [5]. However, no method or agent has yet been proven to completely prevent adhesion formation after surgery.

Oxidized regenerated cellulose (ORC) (Interceed) is the first generation mechanical barrier agent used on the damaged visceral peritoneum and was approved by the US Food and Drug Administration (FDA) for the prevention of post-surgical adhesions [5]. Many experimental studies have shown it to have a protective effect against adhesion formation [9], making it a frequently used clinical agent [10]. Its total absorption time from the abdomen is 2 weeks [11-14].

Trehalose (TRZ) is a natural disaccharide consisting of two glucose molecules [11, 12]. It is used for organ preservation during transplantation, treatment of dry eye syndrome [12, 13] and in different sectors such as the food and cosmetics industry [13]. The protection of biological molecules and the cell membrane can be explained by 3 theories: Water replacement, glass transformation, and chemical stability [15]. In experimental studies, it has been said to have a protective effect against adhesion. Absorption time from the abdomen is thought to be 1 week [13, 15].

Human Amniotic Fluid (HAF) contains stem cells, dead tissue cells, hyaluronic acid (HA), growth factors (fibroblast growth factor (FGF), insulin like growth factor I and II (IGF-I and IGF-II), epidermal growth factor (EGF) etc.), fibrinolytic factors (Plasminogen activator inhibitor -1 (PA-1), and tissue plasminogen activator (t-PAI), etc.) [16, 17]. It is said that the densities of these factors, proteins and cells change according to the gestation period [18]. Various experimental studies have been carried out on adhesions and wound healing in tissues such as the nerves, tendons, sclera, and the abdomen [19, 20]. However, no clear information was published about the absorption time of HAF from the abdomen.

In this study, we comparatively investigated the effects of intraperitoneal ORC, TRZ, and HAF use on adhesion prevention after gynecological operations.

Materials and methods

This study was approved by the local ethics committee of the Yüzüncü Yıl University, Faculty of Medicine in Van, Turkey for the use of laboratory animals and performed at the Experimental Surgical Training and Education Center at the same hospital (Approval number: 2015/06-12 and Date: 30.04.2015)

Animal maintenance and treatment

In this study, twenty-four healthy adult (aged 8-10 weeks) female albino rats weighing 190-240 grams were used. Per the institutional review board's guidelines for animal care, all animals were kept at 22-28°C degrees, with 14-hour light and 10-hour dark cycles. They had access to as much clean water and food as they wanted. Fresh water and standard rodent food pellets were always made available. A power analysis was performed to calculate the minimum sample size required for this study (alpha error = 0.05 and 1-beta =0.8), which revealed that at least 12 uterine horns were required for each study group.

Twenty-four rats were divided into 4 groups using a computer-based system. Animals were anesthetized intramuscularly with a mixture of ketamine hydrochloride (i.m 40 mg/kg 10% Alfamine) and xylazine hydrochloride (i.m 2 mg / kg 2% Alfazin). Before the surgery, the skin of the abdomen was shaved off and cleaned with 10% povidone iodine solution. The abdomen was entered through a 3 cm vertical incision starting from the top of the urethral opening.

As described by Kaya et al. [21] five standard lesions were made on the antimesenteric side of each uterine horn with a 10-Watt bipolar cautery [22, 23]. The same surgical procedure was performed in all rats. In Group 1 (Control), 2 ml of distilled water was poured into the abdomen and waited 1 minute to prevent possible dry air damage. In Group 2 (ORC), 1 cm^2 Oxidized Regenerated Cellulose adhesion barrier (Interceed; Ethicon Inc., Somerville, New Jersey) was placed on the damaged site of the uterus and tuba, then moistened and fixed by adding 1 drop of distilled water. In Group 3 (TRZ), 2 ml of pre-prepared 3% trehalose solution was poured onto the damaged area with a waiting time of 1 minute. In Group 4 (HAF), 2 ml of the prepared human amniotic fluid was poured on the damaged area with a waiting time of 1 minute. The abdominal incision was closed in two layers in all groups. The musculoperitoneum and fascia were closed with simple separated sutures of 4/0 polyglactin (Vicryl; Johnson and Johnson Co, Ethicon Limited, UK). The skin was closed with simple separated sutures of 4/0 polyglactin. After the animals recovered from surgery, they were housed separately under controlled temperatures of 22–28°C with 14-hour light and 10-hour dark cycles with food and water *ad libitum*. The surgery was limited to approximately 10 minutes for each rat to prevent the tissue from drying at room temperature [21, 23]. All surgical procedures were performed by the same surgeon (N.C), who has 10 years of experience in gynecology and obstetrics, and an Obstetrics and Gynecology resident.

Preparation of Oxidized Regenerated Cellulose, Human Amniotic Fluid and Trehalose Solution

Before the surgery, 1 cm² layers were prepared using the commercial ORC brand (Interceed; Ethicon Inc., Somerville, New Jersey) for each rat. Murine amniotic fluid is considered to inhibit xenogeneic antigen response. However, we used human amniotic fluid in this study because murine amniotic fluid is difficult to centrifuge and protect from contamination. Human amniotic fluid (HAF) was obtained in a sterile manner from seronegative, voluntary pregnant patients during their elective cesarean delivery in the 3rd trimester after obtaining informed consent in accordance with the principles of the Helsinki Declaration. Amniotic fluid was centrifuged at 3000 rpm for 15 minutes to separate the cell component. The smears were prepared to ensure that the cells were extracted, stained with the standard Giemsa method, and examined under a light microscope. Samples were frozen at -80 °C and stored [24] with Trehalose dihydrate ($C_{11}H_{22}O_{11} \cdot 2H_2O$, MW: 378.3 g/M), purchased from a biochemical laboratory (Merck Co., Istanbul, Turkey). Trehalose (30 g) was dissolved in 1000 ml distilled water with electrolytes (0.2 g/L of calcium chloride hydrate, 0.3 g/L of potassium chloride, 6.0 g/L of sodium chloride, and 3.1 g/L of sodium lactate) and prepared as stated in the previous study [25]. These solutions were autoclaved and used under sterile conditions. The percentage of trehalose in solution (3%) was selected based on a previous study [25].

Adhesion scoring, tissue sample collection and histopathological analysis

The animals were sacrificed 30 days later by the decapitation method. Leach et al. [26] adhesion scoring system was used for macroscopic (clinical) adhesion scoring (Table 1, Figure 1 (C1, C2). The researcher with an experimental research certificate (an obstetrician with 10 years of experience) who was blinded to the group assignments of the animals evaluated the adhesions according to the spread, severity, and degree of adhesions between the uterine horn and adjacent tissues. Adhesion spread between the uterine horn and adjacent intra-abdominal tissues were scored as follows: 0= no uterine adhesion; 1 = 1%–25% involvement; 2 = 26%–50% involvement; 3 = 51%–75% involvement; and 4 = 76%–100% involvement. Adhesions were further characterized on gross examination for severity as follows: 0 = no adhesions; 1= film-like avascular; 2 = vascular or opaque; and 3 =cohesive attachment of uterine horns to each other or other abdominal structures. The degree of adhesion formation was evaluated with the following adhesion scores: 0 = no adhesions; 1 = adhesion separated from the tissue with gentle traction; 2 = requiring moderate traction; and 3 = requiring sharp dissection.

Adhesions were also examined histopathologically by a pathologist with 10 years of experience and graded for inflammation and fibrosis using previously published grading scales [27] (Table 1, Figure 1) (H1, H2). The edges of adhesion tissue were fixed in 10% formaldehyde for 72 hours, underwent a routine tissue preparation procedure, and were embedded in paraffin. The tissues were examined in 4-micron-thick sections. All sections, after staining with Hematoxylin & Eosin and Masson trichrome, were investigated under a light microscope (Zeiss axioskop 40 Carl Zeiss Göttingen, Germany) and photographed (AxioVision 3,1 Zeiss axioplan 2 imaging Germany, Göttingen). Inflammation was scored as follows: 0 = no inflammation; 1 =

presence of giant cells, occasional lymphocytes, and plasma cells, 2 = presence of giant cells, plasma cells, eosinophils, and neutrophils, and 3 = presence of many inflammatory cells and micro-abscesses. The amount of fibrosis was scored as: 0 = no fibrosis; 1 = minimal, loose; 2 = moderate; and 3 = florid dense. The main outcome measures were spread, severity and degree of adhesions, total adhesion scores, number of adhesion-free uterine horns, and histopathological characteristics (inflammation and fibrosis) of adhesions.

Table 1: The extent, severity, degree, inflammation and fibrosis scoring system of the adhesions

| Score | Macroscopic Adhesion Score | | | Histopathological Score | |
	Extent	Severity	Degree	Inflammation	Fibrosis
0	No adhesion	No adhesions	No adhesions	No inflammation	No fibrosis
1	1–25%	Filmy avascular	Separated from tissue with gentle traction	Giant cells, occasional lymphocytes and plasma cells	minimal, loose
2	26–50%	Vascular or opaque	Requiring moderate traction	Giant cells, plasma cells, eosinophils and neutrophils;	moderate
3	51–75%	Cohesive attachment	Requiring sharp dissection	many inflammatory cells and microabscesses	florid dense
4	76–100%	-	-	-	-

Figure 1: C1 and C2 show examples of clinic adhesion of uterine horn (arrows) in the control group (yellow dot: uterine horn). H1 shows many inflammatory cells with minimal infiltration at the edge of adhesion (hematoxylin and eosin, Bars = 200 µm). In H2, increase of fibrosis is seen at the edge of adhesion (Masson Trichrome, Bar = 200 µm)
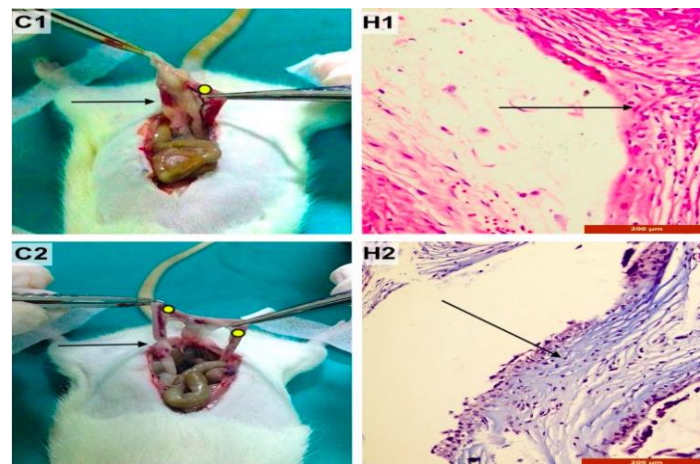
Statistical analysis

Statistical analysis was performed using IBM SPSS (Statistical package for Social Sciences for Windows v22.0 licensed to University of California Davis, USA). Descriptive statistical methods (mean, standard deviation, median, min–max measurements) were used for data analysis. The Kruskal–Wallis test was used to compare differences in scores between the groups, and the Bonferroni corrected Mann–Whitney U test was used to compare differences between the subgroups. A *P*-value of <0.05 was considered statistically significant.

Results

Total macroscopic (clinical) adhesion formation scores were evaluated for all groups. The total clinical adhesion scores were 10.1 (1.72) in the control group, 6.5 (1.64) in the ORC, 3.8 (1.16) in the TRZ, and 4.8 (0.75) in the HAF group. The extent (*P*<0.05), severity (*P*<0.05), degree (*P*<0.05) and total adhesion (*P*<0.05) scores of the control group were significantly higher than those of the ORC, TRZ and HAF groups. Extent (*P*=0.007) and total adhesion (*P*=0.019) scores significantly differed between the ORC and TRZ groups, while severity (*P*=0.136) and degree (*P*=0.760) scores were similar.

Table 2: The differences of macroscopic (clinic) and histopathological scores between the study groups

| | Group 1 (Control) | Group 2 (ORC) | Group 3 (TRZ) | Group 4 (HAF) | P-value | | | | | |
Number of uterin horn	12	12	12	12	I-II	I-III	I-IV	II-III	II-IV	III-IV
Macroscopic Adhesion Score	mean (SD) (range)	mean (SD) (range)	mean (SD) (range)	mean (SD) (range)						
Extent	3,5 (0.54) (3-4)	2.5 (0.54) (2-3)	1.3 (0.51) (1-2)	1.6 (0.51) (1-2)	0.024*	<0.001*	<0.001*	0.007*	0.081	0.99
Severity	3.3 (0.51) (3-4)	2.1 (0.75) (1-3)	1.3 (0.51) (1-2)	1.6 (0.45) (1-2)	0.015*	<0.001*	<0.001*	0.136	0.924	0.99
Degree	3.3 (0.81) (2-4)	1.8 (0.75) (1-3)	1.1 (0.75) (0-2)	1.5 (0.54) (1-2)	0.011*	<0.001*	0.002*	0.760	0.99	0.99
Total	10.1 (1.72) (8-12)	6.5 (1.64) (5-8)	3.8 (1.16) (3-6)	4.8 (0.75) (4-6)	0.001*	<0.001*	<0.001*	0.019*	0.295	0.99
Histopathological Score	mean (SD) (range)	mean (SD) (range)	mean (SD) (range)	mean (SD) (range)						
Inflammation	2.5 (0.54) (2-3)	1.6 (0.51) (1-2)	0.6 (0.51) (0-1)	0.8 (0.4) (0-1)	0.055	<0.001*	<0.001*	0.015*	0.55	0.99
Fibrosis	2.8 (0.40) (2-3)	1.8 (0.4) (1-2)	0.8 (0.40) (0-1)	1 (0) (1)	<0.001*	<0.001*	<0.001*	0.001*	0.003*	0.99

* $P<0.05$ was considered statistically significant. ORC: Oxidized regenerated cellulose, TRZ: Trehalose, HAF: Human Amniotic Fluid

The mean histological inflammation scores in the control, ORC, TRZ and HAF groups were 2.5 (0.54), 1.6 (0.51), 0.6 (0.51) and 0.8 (0.4), respectively. Inflammation was significantly increased in the control group compared to the other groups ($P<0.05$), except the ORC group ($P=0.055$). Fibrosis score was higher in the control group compared to the other groups ($P<0.05$). There were significant differences between the ORC and TRZ groups in terms of inflammation ($P=0.015$) and fibrosis scores ($P=0.001$). Inflammation and fibrosis scores of the TRZ and HAF groups were significantly lower compared with those of the control and ORC groups (Table 2, Figure 2).

Figure 2: Subgroup analysis of the study groups for macroscopic and histopathological scores (Error bars represent 95% confidence intervals)
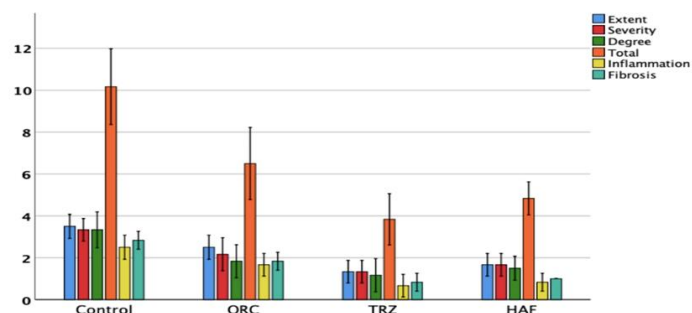
Discussion

Abdominal adhesions occurring after gynecological operations not only cause morbidity and mortality, but also increase health expenses [3, 28]. Complications caused by pelvic adhesions in the United States are estimated to cost $ 1.3 billion annually [28]. These economic costs and complications have directed surgeons to use more advantageous surgical (laparoscopic, robotic) and medical methods (barrier, steroid, anti-inflammatory agents) to reduce adhesions. The cost of synthetic materials (synthetic barrier, gel) currently used in the clinic to reduce adhesions is remarkably high. For this reason, research for more efficient or similar but cheaper methods must continue.

In the literature, ORC, which we also use in our clinic, is reported to reduce adhesions in intrauterine, uterine horn, intestinal, pericardial, pleural and tendon repair models, although the same results were not obtained for adhesions between the thyroid and the skin [9]. Its adhesion prevention potential has been confirmed by many studies [5, 8-10, 26, 29]. However, in the presence of blood, some disadvantages have been reported, as their anti-adhesion effects are reduced and they can slip from the damaged area [29]. In our study, adhesion was decreased in the ORC group.

The autophagy feature of TRZ reduces myocardial fibrosis and conjunctival fibrosis in myocardial infarction [5, 13], while it has no effect on inflammation [30]. It has been reported that 7% TRZ used in the rabbit hysterectomy model is effective in minor injuries but not in major injuries [14, 31]. After dry air damage in human mesothelial cell culture, 3% TRZ was shown to reduce mesothelial cells and adhesions [25]. We also used 3% TRZ in this study and observed that TRZ reduced adhesions. At the end of 30 days, inflammation and fibrosis were the lowest in the TRZ group compared to other groups. Inflammation is expected to decrease in all groups within 30 days; however, we think that the reduction of fibrin gel, which is permanent after inflammation, and the decrease of fibrosis as a result, are important preventors of adhesion. Furthermore, TRZ's crystal structure may have increased its effectiveness by creating a barrier on the tissue.

Cells, proteins, and small molecule factors are found in HAF. Most of its protein content is made up of hyaluronic acid [17, 32]. HAF has been reported to contain hyaluronic acid stimulating activators (HASA) as well [17, 19] and reduces fibroblast activity and fibrin deposits in serosal surface injuries

[18]. In a rat study, HAF decreased intra-abdominal adhesions [33]. In another study, amniotic fluid spilled during a cesarean section did not have an adhesion preventing effect [34]. It has been reported that adhesions are reduced with rat amniotic fluid after hysterectomies in rats [18]. In the adhesion model made in rats, cattle amnion fluid was used and tried in three ways: Raw form, cell-free form, and cell and protein-free form. After the second surgery, the score was the same as the first surgery in all groups. After the third surgery, adhesions increased in the cell-free amniotic fluid group compared to the second scoring, and the adhesions in the cell and protein-free amniotic fluid group was decreased [24]. Cell-free HAF was used in our study, and we observed that HAF and TRZ decreased the adhesions equally. The adhesion scores of all groups were less than that of the control group, and the total adhesion score of TRT was lower than that of ORC. The TRZ and HAF groups were similar in terms of clinical and histopathological adhesion scores ($P>0.05$). We think that HA in HAF acts as a barrier and provides anti-adhesion with the proteins and factors it contains.

Limitations

In this study, we did not fully describe the most active substance in the HAF used. In addition, we used human amniotic fluid, which is genetically different from that of rats. Also, if ORC slides from the surface it adheres to, its effectiveness decreases because it is in film form. Unlike ORC, TRZ and HAF were liquids. Most of the previous studies took 7 and 14 days. We think that our study lasting 30 days is useful in evaluating late-stage adhesion.

Conclusion

While the 3% TRZ reduces adhesion clinically and histologically with its autophagic feature and the crystal barrier on the tissue, HAF does the same by acting as a barrier due to hyaluronic acid and anticoagulant-anti-inflammatory factor balance. We think that further studies on the combination of TRZ and HAF may show improved adhesion prevention properties.

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The effect of uterine and spiral artery Doppler velocimetry in predicting miscarriage in threatened miscarriage patients

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Abstract

Background/Aim: Doppler sonography was used to investigate the effect of abnormal placentation on early and late pregnancy complications with conflicting results on changes in uterine blood flow and spiral arteries in early pregnancy. This study aimed to compare the uterine and spiral artery Doppler findings between healthy pregnant women and patients with threatened miscarriage.

Methods: In this prospective case-control study, the uterine and spiral artery Doppler findings of 60 patients with threatened miscarriage between 12-20 weeks of gestation were compared with those of 60 healthy pregnant women at similar gestational weeks. Resistance index, spiral artery pulsatility index, systolic/diastolic ratio, and uterine artery Doppler values were evaluated.

Results: The patients in the threatened miscarriage group had a higher mean age than those in the control group ($P<0.001$). No significant difference was found between the groups in terms of uterine artery and spiral artery resistance index, systolic/diastolic ratio, and pulsatility index values ($P>0.05$ for each).

Conclusions: Our results showed that there was no significant difference between the indexes of spiral and uterine artery in Doppler ultrasonography. Further studies are needed to evaluate uterine vascular bed alterations to predict the threatened miscarriage prognosis in the first trimester.

Keywords: Resistance index, Pulsatility index, Spiral artery Doppler, Threatened miscarriage, Uterine artery Doppler

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Introduction

Based on the definition of the World Health Organization, miscarriage is defined as the expulsion of all or part of the embryo, fetus, or its attachments outside the uterine cavity within the first 20 weeks of pregnancy. Miscarriage is a common pregnancy complication that occurs in approximately 15% of clinically defined pregnancies [1]. After the pregnancy is detected on ultrasound, this rate decreases to 1.6-6.7% on average [2, 3]. Threatened miscarriage means the occurrence of vaginal bleeding when the cervix is closed, and the fetus is in the uterine cavity during pregnancy. Pelvic pain may or may not accompany the threatened miscarriage. It has been reported that the risk of miscarriage is 2.5 times higher in patients suffering from threatened miscarriage, which is of foremost importance for families' and women's psychological statuses [4].

Extravillous trophoblast should invade the myometrium, maternal decidua, and blood vessels for healthy placentation [5, 6]. With the use of Doppler sonography, the effect of abnormal placentation on early and late complications of pregnancy has been investigated. A non-invasive method that evaluates uteroplacental circulation is the high-frequency transvaginal Doppler sonography. Abnormal velocity waveforms in early pregnancy are related to pregnancy complications, including preeclampsia and intrauterine growth retardation (IUGR) [7, 8]. Few studies have examined the pulsatility index (PI) of the uterine artery, especially under 11 weeks [9]. There are conflicting results regarding changes in the uterine blood flow and spiral arteries in early pregnancy. In many studies, power analysis shows that the number of patients is insufficient. This study aims to compare the uterine and spiral artery Doppler findings between healthy pregnant women and patients with threatened miscarriage.

Materials and methods

Ethics Committee approval was obtained from the Ethics Committee of Beykoz University, Turkey (Permission granted/CAAE number: 30/09/2019 Decision no:1). This prospective case-control study was conducted in accordance with the Helsinki Declaration, in a tertiary hospital between October 2019 and June 2020.

Sociodemographic data such as BMI and age, parity, history of miscarriage, and gestational weeks of the patients were recorded. Sixty volunteers with threatened miscarriages between the 12th-20th gestational weeks admitted to the Obstetrics and Gynecology Department were included in the study. Transvaginal ultrasonography is our routine evaluation in patients presenting with bleeding in early gestational weeks. Transvaginal ultrasonography, which was routinely performed at the time of hospitalization, and uterine and spiral artery Doppler ultrasonography were performed in lithotomy position in 60 volunteering patients between the 12th-20th weeks of pregnancy, and the results were compared with 60 healthy pregnancies at similar gestational weeks. Exclusion criteria included patients with ectopic pregnancy, multiple pregnancy, miscarriages, hypertension, diabetes, immunologic, renal, hematologic, or heart diseases. Doppler ultrasound was performed with the same persons (N.T.O and T.G) in each hospital with the same type of ultrasound device (Siemens, Acuson S1000 Ultrasound System).

The Doppler scanner is compatible with color, has spectral Doppler capacity and a convex-array transducer of 12-MHz. Fetal anomalies, crown-rump length (CRL) measurement, and pregnancy viability were assessed and recorded. The pulse repetition frequency was 2.5 kHz and the high-pass filter was set at a minimum. For Doppler sonographic examination, the maximum attainable mechanical and thermal indices were 1.0 and 1.2, respectively. The sampling gate size was adjusted to be 2 mm. The midsagittal uterine section was visualized and the cervical canal was observed. The probe was not moved laterally until the paracervical vascular plexus was visualized. After color Doppler initialization and detection of the uterine artery, cranially turning the probe caused it to ascend toward the uterine corpus. There were records of the measurements of the uterine artery with spectral Doppler before it branched into the arcuate artery. Once the angle of insonation was below 30º, a spectral Doppler gate appeared over the vessel. To update the tracing, at least three consecutive flow velocity waveforms with adequate quality were verified through measurements of the bilateral uterine artery including pulsatility index (PI), systolic/diastolic (s/d) ratio, and resistance index (RI). There were spiral arteries in the medial third myometrium. The lowest feasible color-gain settings were examined with Doppler ultrasonography. The gain was gradually increased to view the flow pattern. Waveforms of the flow velocity were recorded after finding the flow. At least three satisfactory waveforms were used to calculate the spectral Doppler values. Spiral and bilateral uterine arteries' RI, PI, and s/d values were saved.

Both Lin's Intraclass Correlation Coefficient (ICC) (two way-mixed, absolute agreement, average measurements) and Concordance Correlation Coefficient (CCC) were used to evaluate intra- and inter-observer generalizability and reliability at 95% Confidence Interval (CI). The first and the second measurements of Operator A were crosschecked to investigate the intra-observer reproducibility, which was evaluated using the mean values of the first and second measurements of each operator. The blinded method was used for the examination three times as follows: Observer A performed the first scan, Observer B performed the second scan to check interobserver reproducibility, and Observer A performed the scan once more to check intra-observer reproducibility. To determine the concordance correlation coefficient (CCC) with adequate precision (95% CI width = 0.20) at ≥0.70 (10), a sample size of 120 individuals was needed. CCC values of <0.70 indicated very poor reproducibility [10].

In a reference study evaluating threatened miscarriage patients, the uterine artery s/d ratio was 5.3 (4.6-6.7) in the threatened miscarriage group and 4.3 (3.5-6.1) in the control group. With the mean of two groups compared with the student t-test, calculation of the sample size with G*Power 3.1 (http://www.gpower.hhu.de/) showed that a minimum of 57 patients per group was needed for 80% power and 0.05 type 1 error. A third-party expert's opinion was used to prevent any potential bias.

Statistical analysis

Statistical analyses were performed with SPSS 23.0 software. Categorical values were presented as numbers and percentages, and continuous data were given as mean, deviation, and minimum-maximum values. To compare the continuous

measurements between groups, independent student t-test analysis was applied to binary variables by controlling distributions. A *P*-value of <0.05 indicated statistical significance in all tests.

Results

One hundred and twenty patients were included in the study voluntarily. The mean age of the patients in the threatened miscarriage group was significantly higher than that in the control group (*P*<0.001) (Table 1). The remaining sociodemographic and obstetric data, namely, parity, history of miscarriage, BMI, and gestational week were similar between the two groups (*P*>0.05) (Table 1). There was no significant difference between the groups in terms of uterine and spiral artery PI, RI, s/d values (*P*>0.05) (Table 2). We found that there was moderate intra-observer reproducibility of the CCCs between 0.92-0.95 and moderate inter-observer reproducibility of the CCCs between 0.91-0.95 in transvaginal ultrasonography performed by experienced operators.

Table 1: Baseline characteristics of studied participants

	Threatened Abortion (n=60) mean(SD)	Healthy Pregnant (n=60) mean(SD)	*P*-value
Age	29.97(6.69)	24.43(5.03)	0.001
Parity	1.98(0.98)	1.57(0.67)	0.080
History of early pregnancy loss (≤12 weeks)	0.18(0.43)	0.24(0.43)	0.619
Body mass index (kg/m²)	26.45(4.41)	24.71(4.10)	0.118
Gestational age (weeks)	14.31(2.19)	14.57(2.27)	0.652

SD: standard deviation

Table 2. Spectral Doppler measurements between groups

	Threatened Abortion (n=60) mean(SD)	Healthy Pregnant (n=60) mean(SD)	*P*-value
Uterine artery PI	1.59(0.31)	1.58(0.36)	0.934
Uterine artery RI	0.70(0.05)	0.71(0.07)	0.536
Uterine artery S/D	4.9(1.44)	4.6(1.28)	0.230
Spiral artery PI	0.51(0.10)	0.51(0.10)	0.792
Spiral artery RI	0.35(0.05)	0.37(0.06)	0.163
Spiral artery S/D	4.16(0.92)	4.05(1.21)	0.576

SD: standard deviation, PI: pulsatility index, RI: resistance index, S/D: systolic/diastolic

Discussion

Uteroplacental circulation is not fully elucidated. There is an association between vascular remodeling disruption on the maternal-fetal surface and complications of pregnancy [11]. It has been reported that intensive vascular remodeling during early pregnancy is important in healthy progression. Determining the uteroplacental vascular changes from implantation until the end of the pregnancy may be diagnostic in the clinical management of early pregnancy loss and pregnancy complications [12]. The resistance index of the spiral artery decreases after the 5th gestational week. This is shown to reduce local arterial resistance in vascular remodeling caused by trophoblast invasion [13]. A study conducted by Pellizzari et al. [14] showed no significant difference in resistance indexes between the 6th-12th gestational weeks, which is in line with our study results. In a study by Özkan et al. [15], no significant difference was found in resistance index, spiral artery pulsatility index, and systolic/diastolic ratio values, but systolic/diastolic ratio was higher in uterine artery values in the miscarriage group. In the study by Roberts et al. [16], it was shown that maternal blood flow to placental intervillous space starts from the 6th week. The uterine artery systolic/diastolic ratio was promising in predicting adverse outcomes. However, although abnormal placentation starts from the beginning of

pregnancy, it can become more evident at the end of the first and second trimesters [15]. There may be very small vascular changes in the uteroplacental circulation in the first trimester, and the uterine artery velocity waveform is changed through its localization. In a few studies evaluating the small vessels of the vascular uterine bed, including the spiral artery and subchorionic vessels, a significant association was reported between abnormal Doppler findings and pregnancy results, while no significant association was found in the other studies [17, 18]. In the study conducted by Ozkaya et al. [19], the increase in the uterine and spiral artery resistance indexes increased the risk of miscarriage, placental abruption, preterm labor, and IUGR in a limited number of cases, which is not in line with our study results. Guedo-Martin et al. [9] reported an age-related reduction of RI and PI values of the uterine artery from 6 weeks to 10 weeks. The study conducted by Özkan et al. [15] reported that uterine and spiral arteries showed different changes in early pregnancy, and spontaneous abortion risk might increase in pregnancies with high spiral artery RI at the 5th and 6th weeks. When spiral artery RI is normal, decreased uterine artery RI in the placental area may occur with a locally developing shunt [20]. Sheehata et al. [21] found no significant difference between the Doppler indices of the uterine artery. The patients' ages were significantly higher in the spontaneous abortion group than in the ongoing pregnancy group, which is consistent with previous studies reporting that inappropriate and inadequate progesterone secretion increases miscarriage rate due to ovarian aging [21, 22]. In our study, age was significantly higher in the threatened miscarriage group and no significant differences were found in the indexes of spiral and uterine arteries by Doppler ultrasonography.

Limitations

Two observers examining the variables can be considered as a study limitation. However, the use of the same quality ultrasound machine has been the factor that improves the reproducibility of the study.

The major strength of this research is the fact that it was conducted with transvaginal measurements, in line with the Guidelines of the International Society of Ultrasound in Obstetrics and Gynecology [23]. The ultrasound scans were entirely detached, observers were blinded to their results, and the results were analyzed and interpreted attentively.

Conclusion

In the first trimester, fetal structural changes are detected most, and hemodynamic evaluation is not given enough importance. There are important limitations of investigating the spiral and uterine artery indexes in the early weeks of pregnancy. There should be more studies to explain the relationship between histological findings of vascular remodeling and spiral artery resistance in Doppler ultrasonography and evaluation of the uterine vascular bed alterations for prediction of the prognosis of threatened miscarriage in the first trimester.

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The relationship between the prevalence of postpartum depression and anxiety, and depression levels in the mothers of premature, and term newborns admitted to a pediatric emergency department

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Abstract

Background/Aim: Postpartum depression is a frequent condition that is seen within 4 weeks after giving birth. In addition to the common symptoms of depression such as low mood, change in appetite, and poor concentration, mothers with postpartum depression also experience guilt about their presumed inability to look after their baby. Preterm birth occurs approximately in 9.4% of all births. Despite this high rate, the effects of prematurity on postpartum depression have not been investigated thoroughly. The aim of this study is to compare the prevalence of postpartum depression in mothers of premature and term newborns, evaluate the relationship between anxiety and depression levels, while determining the sources of stress in recent mothers.

Methods: The mothers who gave birth in the last three months to 50 premature and 50 term newborns who were admitted to the pediatric emergency service of a Training and Research Hospital between August 2017 and November 2017 were included in this cross-sectional type study. The participants filled out the sociodemographic and clinical data forms and responded to the Edinburgh Postpartum Depression Scale, the Beck Depression Inventory, and the Beck Anxiety Inventory. The results of the scales were statistically analyzed using SPSS 19.0 package program.

Results: According to the Edinburgh Postpartum Depression Scale, 32% of the mothers of preterms and 28% of the mothers of term newborns were diagnosed with postpartum depression. In 58% of the mothers of preterms and 68% of the mothers of terms, minimal depression was present. When the cases were grouped according to the results of the Beck Anxiety Inventory, mild anxiety was found in 34% of the mothers of preterms, while mild anxiety was present in 18% of the mothers of term newborns. Comparison of the mothers of preterm and term newborns according to postpartum depression, Beck Depression Inventory, and the Beck Anxiety Scale revealed no statistically significant differences between the groups ($P>0.05$).

Conclusion: Although the prevalence of postpartum depression and mild anxiety was higher in mothers of premature children, the results were not statistically significant. Studies with larger samples or meta-analysis of several studies may yield more significant results which may enable allocation of limited mental health resources to the mothers of premature children.

Keywords: Postpartum depression, Preterm, Term

Introduction

Depression is a syndrome characterized by deep sadness (sometimes accompanied by anxiety), slowing and stagnation in thoughts, speech, movements, and physiological functions, as well as feelings and thoughts of worthlessness, weakness, reluctance, and pessimism [1]. In DSM-5, anxiety, atypical, catatonic, melancholic, mixed, peripartum, psychotic, and seasonal subtypes were used to provide more diagnostic specificity. Perinatal depression is a broad term that refers to an episode of major or minor depression with the onset during pregnancy or within the first four weeks in the postpartum period, as defined in the DSM-5 criteria [2].

DSM-5 restricted the use of this term by emphasizing that the onset of symptoms should occur within the first four weeks in the postpartum period; however, other sources suggested that the duration might extend up to 3, 6, or even 12 months postpartum [3]. Symptoms of postpartum depression include feelings of worthlessness, anxiety, guilt, concerns about the baby, tearful mood, slow movement and speech, agitation, or hyperactivity, eating problems, sleep problems, confusion, forgetfulness, emotional instability, feelings of anger, hopelessness, and inadequacy, thoughts about death and suicide, reduced concentration and decision-making ability, and decreased interest in sexual activities [4].

Postpartum unipolar major depression episodes vary according to their severity. The severity is important for determining a treatment regimen. A study on patients with postpartum unipolar major depression determined more severe episodes according to the onset of depressive symptoms during pregnancy, an average of 20 points in EPDS, and the presence of anxiety symptoms, suicidal thoughts, and obstetric complications [5]. Also, a previous study compared postpartum depression scores in patients with planned and emergent cesarean sections and found higher scores in EPDS in women who underwent emergent cesarean section [6].

The diagnostic criteria for postpartum major depression are the same as those used in the diagnosis of non-puerperal major depression. In clinical practice, the term postpartum depression is used to describe depression that begins within 12 months of birth [7]. The patients who get a mean of 11 and 15 points from EPDS are considered to have mild and moderate episodes, respectively [5]. Psychotherapy is recommended as an initial therapy for mild to moderate postpartum unipolar major depression [8]. Antidepressants are considered as a reasonable alternative if psychotherapy is not available, is not successful, or is rejected, or if the patient has previously responded to antidepressants [9]. The patients who got a mean of 20 points from EPDS were considered to have a severe episode [10]. For breastfeeding patients with severe postpartum unipolar major depression, access to antidepressants is easier than psychotherapy, and antidepressant use was recommended in numerous practice guidelines [11].

In the current study, we aimed to compare the prevalence of postpartum depression in mothers of premature and term newborns and determine the relationship between anxiety and depression levels in addition to the sources of stress in recent mothers.

Materials and methods

The research was conducted as a cross-sectional study in the inpatient clinics of the department of pediatric emergency in Health Sciences University Umraniye Training and Research hospital between August 2017 and December 2017. The cases were chosen among volunteers who were at least graduates of elementary school and gave birth in the last six months. Signed informed consents were obtained from all participants, and the institutional ethics committee of Umraniye Research and Education Hospital (decision date 20-07-2017; no: 108) approved the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

The exclusion criteria consisted of being illiterate, having cognitive deficits at a recognizable level during the initial interview, having a very poor general medical condition that was apparent during the initial interview, and having a diagnosed psychotic disorder.

Because there was no similar previous study, a pilot study was performed with 10 subjects from each group. The effect size was determined using Edinburgh Postpartum Depression Scale. According to the results, 34 subjects were required in each group to reach an alpha value of 0.05 and 1-beta value of 0.20 (Table 1). We included 50 subjects from each group.

The participants filled out the sociodemographic and clinical data forms and responded to the Edinburgh Postpartum Depression Scale, the Beck Depression Inventory, and the Beck Anxiety Inventory. The socioeconomic questioning included the demographic features of the parents (age, education, employment, economic status, social security, residency, migration), and marriage history (order of marriage, decisions made for marriage, family type, consanguinity). The clinical data obtained by questioning the obstetrical history and the recent pregnancy-related factors included the number and outcomes of previous deliveries, the presence of assisted reproduction vs. planned pregnancy, the routine follow-up of pregnancy, multiparity, maternal smoking and chronic diseases, the delivery time and method of delivery, maternal health problems during labor, the gender, weight, breastfeeding status of the recent newborn, the perceived difficulty of baby care and perception of being a good mother.

Statistical analysis

Statistical analyses using the Statistical Package for Social Sciences for Windows version 19 software (SPSS) were performed to evaluate the data gathered from each subject. Independent Samples t-test and the Chi-Square tests were used to analyze the parametric and nonparametric data.

Results

The study was completed with one hundred subjects who were divided into two groups, each with fifty mothers who gave birth either to preterm (preterm group) or term newborns (term group). The data retrieved from sociodemographic forms indicated that the majority of marriages (96%) were officially declared, while the remaining (4%) were declared religiously. All preterms were born to officially married couples. In 94% of the cases, the present one was the first marriage. The decision to marry was freely made in most of the marriages in both groups (62% for each), while in 38% in both groups, it was an arranged marriage.

The frequency of consanguinity was 16% and 24% between the parents of preterm and term newborns, respectively. The family structure was nuclear in most of both groups (78% in preterms and 84% in terms). The mean age of mothers and their spouses and the mean age at marriage in both groups were shown in Table 1.

Table 1: The results of the power analysis

	Groups		The difference between the means	α	1- β
	Preterm	Term			
Postpartum Depression	8.90 (5.04)	5.70 (4.27)	3.20		0.05	0.20
Sample size (n)	34	34			

We found that the majority of the mothers in both groups (36% in preterms and 44% in terms) were graduates of primary school and unemployed (68% in preterms and 70% terms). The income of most families in both groups (48% in preterms and 46% in terms) were middle-lower level. Most families (94% in both groups) were found to have social security. Residency in an urban area was the most common setting in both groups (92% in each), while 26% and 30% of the preterm and term families, respectively, were immigrants. The region of residency and the distribution of all descriptive features in both groups were summarized in Table 2.

Table 2: The distribution of descriptive characteristics of the cases included in the study

	Preterm n=50 n (%) Mean (SD)	Term n=50 n (%) Mean (SD)
Age	28.8 (6.1)	29.1 (5.3)
Spouse's age	32.3 (5.3)	32.1 (6.1)
Age of marriage	23.2 (3.8)	22.9 (5.4)
Education		
Literate	7(14)	7(14)
Primary School	18(36)	22(44)
High School	13(26)	14(28)
University	12(24)	7(14)
Employment Status		
Employed	16(32)	15(30)
Unemployed	34(68)	35(70)
Economic status		
Lower	7(14)	10(20)
Middle-lower	24(48)	23(46)
Middle-upper	19(38)	17(34)
Social security		
Present	47(94)	47(94)
Absent	3(6)	3(6)
Place of residence		
Urban	46(92)	46(92)
Rural	4(8)	4(8)
Migration status		
Yes	13(26)	15(30)
No	37(74)	35(70)
Region		
Middle	6(12)	5(10)
South	2(4)	0
North	12(24)	15(30)
East	19(38)	22(44)
West	11(22)	8(16)
Family type		
Nuclear	39(78)	42(84)
Extended	11(22)	8(16)
Marriage type		
Self-selected marriage	31(62)	31(62)
Arranged marriage	19(38)	19(38)
Consanguineous marriage		
Present	8(16)	12(24)
Absent	42(84)	38(76)

The information gathered about the previous pregnancies indicated that the mean number of deliveries in preterm and term groups was 1.9 (1.1) and 1.82 (1.0), respectively. The rates of stillbirth were 6% and 8% in preterm and term groups, respectively. The data related to the recent pregnancy showed that in 8% and 6% of the preterm and term groups, the pregnancy occurred with assisted reproduction techniques, and routine follow-up was performed in 92% of the preterm and 100% of the term pregnancies. The rates of multiple pregnancy were 6% and 4% in preterm and term groups, respectively. The presence of chronic diseases and smoking in the preterm group mothers (8%

and 4%, respectively) were higher than the mothers in the term group (4% and 0%, respectively). In 92% of the term group, no maternal health problems were reported, while 32% of the mothers who gave birth to preterm newborns had health problems during delivery. Fifty and forty percent of the mothers in the term and preterm groups had normal spontaneous vaginal delivery. The gender of the newborns was female in 52% and 40% of the term and preterm groups, respectively. Health problems during the newborn period occurred in 12% and 42% of the terms and preterms, respectively. All demographic and clinical parameters related to previous and current pregnancies, the gender, weight, breastfeeding status of the preterms and terms in the study groups, the perceived difficulty of caring for the baby, and the perception of being a good mother were shown in Table 3.

Table 3: The distribution of the cases according to pregnancy features

	Preterm n (%) Mean (SD)	Term n (%) Mean (SD)
The number of deliveries	1.9 (1.1)	1.82 (1.0)
The number of living children	1.9 (1.1)	1.7 (1.0)
Curettage	5(10)	5(10)
Abortus	11(22)	12(24)
Stillbirth	3(6)	4(8)
Multiple pregnancy	3(6)	2(4)
Planned pregnancy	38(76)	41(82)
Pregnancy follow-ups	46(92)	50(100)
Chronic disease	4(8)	2(4)
Smoking	8(16)	0
Assisted reproduction	4(8)	3(6)
Gender preference	9(18)	7(14)
Sex (female)	20(40)	26(52)
Type of delivery (Normal Vaginal Delivery)	20(40)	25(50)
Time of delivery (daytime)	22(44)	31(62)
Maternal health problem during birth (no)	32(64)	46(92)
Newborn problem after birth	21(42)	6(12)
Baby weight		
Below 1500gr	10(20)	0
1500-2500 gr	18(36)	4(8)
Above 2500 gr	22(44)	46(92)
Breastfeeding	40(80)	48(96)
Baby care (difficult)	12(24)	14(28)
Thinks she is a good mother	46(92)	49(98)

We did not observe any significant difference in the rates of postpartum depression between the groups (in the mothers of 32% of the preterms vs. 28% of the terms) (P=0.234). The severity of depression measured by the Beck Depression Inventory revealed that a minority of mothers in both groups (16% in preterms and 6% in terms) suffered from moderate depression (P=0.653). The responses of participants to the Beck Anxiety Inventory showed that severe anxiety was experienced only in 6% of the mothers in the term group while no mothers had severe anxiety in the preterm group (P=0.135) (Table 4).

Table 4: The comparison of postpartum depression and the Beck Anxiety Inventory scores between the preterm and the term cases

	Preterm n (%) Mean (SD)	Term n (%) Mean (SD)	P-value
Postpartum Depression	16(32)	14(28)	0.234
Beck Depression Inventory			0.653
Minimal	29(58%)	34(68)	
Mild	13(26)	13(26)	
Moderate	8(16)	3(6)	
Beck Anxiety Inventory			0.135
Mild	17(34)	9(18)	
Moderate	5(10)	8(16)	
Severe	0	3(6)	

Discussion

Depression is an affective disorder with a high and increasing prevalence [1]. As it can be affected by the lifestyle, depression itself may also affect the lifestyle. Not only the patient but also the people in close proximity to the patient could be affected by depression at varying degrees as in other psychiatric

disorders. Previous research demonstrated that depression occurred more frequently in women in the reproductive years, and especially childbirth and puerperium increase its frequency [12]. In other words, birth and puerperium, which are actually known as physiological events, may trigger depression [13]. The mood changes, which are due to variations in the serum levels of hormones in pregnancy, sometimes progress to a pathological state and become a disorder. The fact that this does not occur in every expectant mother leads to self-questioning for the standards of living. In addition, events experienced during labor and after the birth of the child can also be triggers for depression.

Postpartum depression is the name given to the mood disorder that can be seen in the first month after birth [2]. In this instance, patients may experience depressed mood with symptoms such as unwillingness, pessimism, decreased appetite, not being able to enjoy life, feeling worthless and powerless, not capable of caring and showing the otherwise required attention and love for their baby, and avoidance of breastfeeding [1]. The prevalence of postpartum depression is 13% in the general population [14]. We found that postpartum depression was present in 32% of the preterm group and 28% of the term group; no statistically significant difference was present between the groups. The higher rates of depression in both groups than the rate of postpartum depression in the general population might be because both groups of mothers had sick children. Having a sick child can also be a predisposing factor for depression.

Preterm delivery and having a premature baby are thought to be triggers for postpartum depression for a mother. The comparison of the mean Beck Depression Inventory scores between the groups revealed that the rates of minimal depression, mild depression, and moderate depression in the preterm group were 58%, 26%, and 16%, respectively, and 68%, 26%, and 6% in the term group, respectively. The comparison of mean Beck Anxiety Inventory scores revealed that the rates of mild, moderate, and severe anxiety in the preterm group were 34%, 10%, and 0%, respectively, and in the term group, 18%, 16%, and 6%, respectively. In the preterm group, the prevalence increased with increasing severity of anxiety and depression. However, in our study, no statistically significant difference was found between the groups. We consider that this result was due to the small sample size and the relevant feature of the group, i.e., the mothers of sick children.

A previous study reported depressive symptoms in 70% of pregnant women, with only 10-16% diagnosed with major depression [15]. In another study, the rate of moderate-severe depression during pregnancy was 3.5-9%, while the rate of postpartum moderate-severe depression was 3.5-16% [16]. Studies on this subject revealed that the rate of depression in patients diagnosed with depression in previous pregnancies or the postpartum period and recovered with treatment was increased by up to three times [17, 18]. Moreover, Forman et al. found that the rate of postpartum depression was high in patients who became pregnant after treatment for non-depression psychiatric diseases [19].

Many studies on depression have found a close relationship between smoking and depression. For example, in a study conducted on 1265 patients in New Zealand, a higher rate of cigarette addiction was found in the major depression group [20].

Also, a study from England found a higher rate of postpartum depression in patients who smoked during pregnancy than in the non-smoking group [21]. The relationship between smoking and depression, which triggers the other, has not been precisely determined. As it is known, cigarette consumption is quite common in patients with schizophrenia because it reduces the drug side effects.

Other parameters thought to be associated with depression are multiparity and the excess number of children. In two large-scale studies, having too many children and high parity increased postpartum depression up to 2-3 times [19, 22].

Low education level is also emphasized as another predisposing factor for depression. A study conducted in Turkey revealed that low education levels, besides having many children, and pregnancies with short intervals were causes of postpartum depression [23]. Similarly, in two large-scale studies from Geneva and Pennsylvania, a close relationship was found between low education level and postpartum depression [24, 25]. Moreover, as can be predicted, many studies have determined that low economic income also triggered postpartum depression [26, 27].

The relationship between breastfeeding and postpartum depression was revealed in many studies [28, 29]. A study found that the cessation of breastfeeding caused guilt feelings in women and triggered postpartum depression. Interestingly, breastfeeding played a great role in the treatment of postpartum depression [4]. A comprehensive study on 14609 women from 32 states in the USA in the context of the Pregnancy Risk Assessment Monitoring System (PRAMS) suggested that breastfeeding avoidance was a result of postpartum depression rather than a risk factor for it. Some authors also suggested reconsidering the effect of antidepressant use on the avoidance of breastfeeding [30].

Breastfeeding is of great importance for the health of both the mother and the baby. Therefore, every mother should breastfeed unless there is a contraindication. However, in the case of postpartum depression, the mother-infant relationship suffers, and the mother refuses to breastfeed. A previous study found a cause-and-effect relationship between the inability to breastfeed due to several reasons and postpartum depression [31]. From a different point of view, there is no doubt that the incapability of breastfeeding can lead to depression in the mother. Therefore, the question of whether smoking or depression were triggering factors reminds of the relationship between the lack of breastfeeding and the postpartum depression. For example, a mother who had a preterm birth and was separated from her newborn due to prematurity-related stay in the incubator might be dragged into depression. Even milking and saving it in a bottle while knowing that it would be given to her baby could often be sufficient to affect her emotional state in a positive way. Therefore, preventing preterm births as much as possible is important in reducing postpartum depression. Psychological support should be provided to mothers who give preterm birth.

Limitations

This study has several limitations. First, the diagnosis of postpartum depression was not made with a clinical interview. In self-rated scales, subjects may aggravate their symptoms which may cause over diagnosis. Although we performed a power analysis before the study and exceeded the required sample size, the higher values in mothers of preterm babies which could not

reach statistical significance was possibly because of small sample size. The main strength of the study was differentiating the effects of having a premature child from the effects of postpartum depression.

Conclusion

We could not determine increased risk of postpartum depression in mothers of premature children although depression and anxiety scores of the mothers of premature children were higher. Studies with larger samples or meta-analysis of several studies may yield more significant results, which may enable allocation of limited mental health resources to mothers of premature children.

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Review

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Does exercise have healing and preventive roles in COVID-19 pandemic?

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Abstract

The COVID-19 pandemic caused by the SARS-CoV-2 virus, which occurred in Wuhan in China on December 31, 2019, spread rapidly to 6 continents and hundreds of countries. Scientists continue to work on effective treatment protocols and vaccine development to stop the spread of this pandemic. Currently, anti-virus strategies are as important as treatment methods. It is known that physical exercise is one of the pillars of a healthy life and reduces the risk of developing non-infectious diseases which endanger the immune system significantly. Besides, regular moderate intensity exercise has preventive effects against cardiovascular diseases, respiratory tract infections, obesity, and diabetes. In this review, we aimed to discuss whether physical activity has a protective effect and present new information to ameliorate the wellbeing of individuals during the pandemic, so they are less affected by COVID-19. From this point of view, experimental and clinical studies on this subject were analyzed. Literature reviews showed that maintaining physical exercise during the COVID-19 outbreak is crucial for the recovery of patients with obesity, lung, and heart diseases. However, it can be said that asymptomatic young and middle-aged individuals with positive COVID-19 tests can overcome the disease more easily and in a shorter time.

Keywords: COVID-19, Exercise, Pandemic

Introduction

Coronavirus (COVID-19) was detected in Wuhan, China in December 2019 [1]. By 23 March 2020, it had become a pandemic with more than 353,000 cases, 15,000 deaths, and 100,000 cases confirmed [2]. By 23 May 2020, there were 5 million 14 thousand cases worldwide, and 328.462 had perished. The number of individuals recovering has exceeded 2 million [3]. Turkey was also affected by the pandemic. As of 15.06.2020, the total number of cases is 179.831, the number of deaths is 4.825 and the number of recovered patients is 152.364. According to these official figures, the infection spread to Turkey later than the other countries [4]. Effective treatments implemented by specialists and healthcare personnel in the pandemic hospitals and intensive care units with adequate respiratory support equipment have enabled the outbreak to be controlled in our country. Countries have implemented serious isolation measures to prevent the COVID-19 outbreak, which dragged people into a sedentary lifestyle. Anxiety, depressed mood, and boredom make it worse [5]. People can perform physical activity and exercise by maintaining social distance at home or outside to reduce the negative effects of isolation, maintain general health and weight control, prevent chronic illnesses from worsening and eliminate the risk of infection [6].

COVID-19 infection

Etiology

Coronaviruses (CoV), a large family which can cause disease in humans and animals, are non-segmented positive-sense, single-stranded ribonucleic acid (RNA) viruses which encompass the Orthocoronavirinae subfamily. They have 4 main genera: α (Alpha), β (Beta), γ (Gamma) and δ (Delta). While γ and δ strains infect birds, α and β strains infect mammals and cause respiratory infections in humans and enteritis in animals [1].

In addition to the 6 types of human coronaviruses (HCV) known to date, the first complete genome of the new genus of coronavirus was identified in bronchoalveolar lavage samples from the first cases of pneumonia observed in Wuhan in addition to three different strains. This isolated new type of coronavirus is the seventh member of the family. The International Committee on Taxonomy of Viruses group recommended that this virus be called Serious Acute Respiratory Distress Syndrome Coronavirus-2 (SARS-CoV-2) [7,8].

Epidemiology

The COVID-19 outbreak caused by the SARS-CoV-2 virus, which occurred in Wuhan, China on December 31, 2019, spread rapidly to 6 continents and hundreds of countries [9]. It was declared as an international public health emergency by the World Health Organization on 30 January 2020. As of January 6, 2021, the total number of COVID 19 cases is 84 474 195, and the total number of deaths is 1 848 704 worldwide [3]. In Turkey, the first case was diagnosed on March 11, 2020. By 29.12.2020, the total number of cases had reached 2.178.580, the number of deaths had reached 20.388 and 2.058.437 individuals had healed [4]. Currently, prevention strategies are at least as important as treatment methods.

Mode of transmission

Although published studies show that various animal species such as pangolin, bat, snake, and turtle may be intermediate hosts in infection, the zoonotic source of SARS-CoV-2 is not known for certain [11]. It is thought that the onset is zoonotic, however, human to human transmission occurs via coughing, sneezing, or speaking. The incubation time of the disease is not yet fully elucidated. Although symptoms often appear within 5 days of virus exposure, the World Health Organization published its status report on February 19, confirming that the average incubation period was extended to 14 days [12]. There are plenty of unknowns in terms of the COVID-19 pandemic.

Clinical

Disease spectrum caused by a coronavirus in humans can range from simple common cold to severe acute respiratory syndrome. It does not have a specific clinical feature that can safely differentiate COVID-19 from other viral respiratory infections. COVID-19 tends to cause more severe disease in the elderly with underlying medical problems. The Epidemiology Working Group of the Center for Disease Control and Prevention in China reported that 81% of patients mildly suffered from the disease (none or non-serious pneumonia), 14% were moderately affected (hypoxia, oxygen saturation <93% or lung involvement in over 50% of sections as detected by imaging within 24-48 hours), and 5% had severe disease (acute respiratory failure, septic shock, multiple organ failure). In all cases, the mortality rate ranged between 2.3% and 5% [13]. In a study on 1099 patients with COVID-19 pneumonia in Wuhan, the most common clinical features observed at the beginning of the disease are in order of frequency are fever (88%), dry cough (67%), fatigue (38%), dyspnea (18.7%), and myalgia (14.9%) [14]. The severity of the disease and its mortality are associated with concomitant cardiovascular diseases, diabetes, hypertension, chronic lung, and kidney disease, and cancers [15]. According to the data in China, the mortality rate was 10.5% in patients with cardiovascular disease, 7.3% in those with diabetes, 6.3% in chronic respiratory failure patients, 6.0% in those with hypertension, and 5.6% in patients with malignancy [16]. Among 355 patients who died due to COVID-19 in Italy, the presence of chronic disease was emphasized as the underlying cause in all cases, except for 3 [17].

The effect of physical exercise on immunity

The effects of exercise on immune functions depends on many variables such as the type of exercise, intensity, severity, duration, and physical fitness level of the individual [18]. Generally, the total leukocyte count increases by 50 percent to 100 percent immediately after a high-intensity exercise. Neutrophils and lymphocytes are the main sources of this increase. When the lymphocyte subgroups are analyzed in detail, it is seen that the natural killer (NK) cells are the most responsive to exercise. While it also increases T8 cells, T4 and B cells are not affected [19]. Physical stress induced by exercise also increases blood concentrations of various stress hormones such as adrenaline, noradrenaline, growth hormone, beta-endorphins, cytokines, and cortisol. These increased levels of hormones take part in the regulation of the exercise-induced immune system. Also, physiological factors such as body temperature, oxygen desaturation, metabolic factors such as glutamine, glucose, and free fatty acid levels play an important role in the effects of exercise on the immune system [20]. It seems more appropriate for those who exercise for a healthy life to choose moderate and stressless exercise types.

Can physical exercise prevent the risk of developing COVID-19?

There is no scientific data to examine the effects of exercise on COVID-19. However, physical exercise is one of the pillars of a healthy life, and therefore the primary component of wellness medicine [21]. It has been shown to significantly reduce the risk excess body mass and non-communicable diseases known to cause systemic inflammation and jeopardize immune function [22]. A study on the 1997 Hong Kong flu pandemic showed that patients who regularly perform low and moderate intensity exercises have a significantly lower risk of mortality than patients who do not [23]. According to Ahmed (2020), studies on rodents show that moderate physical exercise reduces susceptibility to respiratory infections and improves antiviral lymphocyte function [24]. Nieman and Wentz (2019) state that the immune system is very sensitive to the duration, intensity, and content of the exercise [25]. Moderate exercises reduce the duration, severity, and incidence of upper respiratory infections [26]. Several epidemiological studies suggest that regular physical exercise causes a decrease in the incidence and mortality of influenza and pneumonia [27]. Studies report that regular participation in moderate and high-intensity physical exercise reduces acute upper

respiratory tract infection by 28% [28, 29]. Significant reductions in the risk of mortality attributed to upper respiratory tract disease, lower respiratory tract disease, and aspiration pneumonia have been reported in athletes, including diabetes mellitus [30]. In the face of this new coronavirus epidemic, the World Health Organization (WHO), Centers for Disease Control and Prevention (CDCP), and other public health advisory organizations (ACSM, AHA) recommend engaging in regular physical activity to maintain physical and mental health and well-being. The health organizations mentioned above state that 150 minutes of moderate-intensity exercises per week can provide a protective effect against viral infections [25-30]. From this point of view, according to exercise scientists, the optimal exercise intensity, frequency, duration, volume, type, and intensity need to be determined.

What should be the exercise model?

During this pandemic, a combined exercise model should be preferred covering basic motor features such as endurance, strength, balance, coordination, and mobility [31, 32]. A 5-day exercise model should aim to preserve strength on 2 days, endurance on 2 days, and balance-coordination on 1 day.

How to determine the intensity of exercise and what should be?

Exercise intensity is determined by how close the heart rate is to the target value, which is best assessed using the maximal heart rate or Karvonen method, as follows:

Maximum Heart Rate= 220-age

Target Heart Rate = % (Maximum Heart Rate – Resting Heart Rate) + Resting Heart Rate, in which % depends on the intensity of exercise. Exercise intensity can also be determined with tests that measure the maximal oxygen consumption capacity (maxVO2), such as 6 minutes walking test, Cooper test, Treadmill Balke test, and Harvard step test [2, 8].

What should be the frequency and duration of exercise?

The Royal Australian College of General Practitioners reports that 150 minutes of exercise per week, 30 minutes of daily moderate intensity exercise which incorporates 2 days of strength training aids in protecting from chronic diseases [33]. Also, WHO and ACSM state that 150 minutes of moderate-intensity exercise per week can be protective against viral infections [33-35].

Exercise program

In Table 1, an exemplary training program was adapted using the opinions of American Sports Medicine [36]. To avoid injuries and perform high-efficiency exercises, warm-ups should be performed at the beginning of each exercise and cooling, at the end.

Warm-Up Exercises: 10 min walking or jog, 5 min stretching
Cooling Exercises: 5 min walking or jog, 5 min stretching

Table 1: Exercise Program [35]

	Aerobic Exercises	Strength Exercises	Balance and Coordination Exercises
Exercise Frequency	2 days a week	2 days in a week	1 day in a week
Exercise Intensity	Moderate Intensity (KAHmax %40-60)	Initial, Strength exercises using body weight and then with light weights	Static and dynamic stretching exercises for 8-10 seconds
Exercise Type	Endurance exercises that appeal to large muscle groups such as walking, jog, cycling	Exercises that appeal to large muscle groups with their body weight, elastic bands, and light weights (sit-ups, push-ups, squats)	Static and dynamic stretching exercises for large muscle groups in the lower and upper extremities (stretching)
Exercise Duration	2x3 sets 8-10 reps	2x3 sets 8-10 reps	8-10 sec and 2 x 3 sets for each exercise
Exercise Volume	60 minutes of exercise in a week	60 minutes of exercise in a week	30 minutes exercise in a week

Conclusion

Unfortunately, there is currently no standard treatment or vaccine for COVID-19. Therefore, virus prevention strategies should be as important as researching for treatment methods in limiting and preventing the spread of the disease. Maintaining the physical activity levels of individuals during the COVID-19 epidemic will be of great importance for the recovery of patients with additional comorbidities, such as the elderly or obese patients, those with lung and heart diseases, both before and after the infection. Also, it is thought that asymptomatic young and middle-aged people with positive COVID-19 tests can overcome this disease more easily and within a shorter time.

Main Points

- Physical exercise is the mainstay of healthy life, and significantly reduces the development of human non-communicable diseases.
- It is stated that regular moderate intensity exercise has important effects on the prevention of many diseases such as cardiovascular diseases, respiratory tract infections, obesity, and diabetes.
- Maintaining the physical exercise levels of people during the COVID-19 outbreak will be crucial for the recovery of patients with obesity, lung, and heart diseases.
- COVID-19 virus prevention strategies should be at least as important as researching treatment methods in limiting and preventing the spread of the disease.
- Young and middle-aged asymptomatic individuals with positive COVID-19 tests can overcome the disease more easily and in a shorter period

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Journal of Surgery and Medicine

A rare cause of abdominal pain: Spontaneous rupture of the spleen

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

Spontaneous spleen rupture (SSR) has a high mortality rate, and numerous factors have been blamed in its etiology. In this case study, the purpose was to discuss a patient diagnosed with SSR in light of the literature. A 62-year-old male patient, who gave verbal permission to be presented in the case report, was admitted to the Emergency Service with abdominal pain, nausea, vomiting, and diarrhea complaints that started the day before. In the Focused Assessment with Sonography for Trauma (FAST) Ultrasonography (USG) of the patient, there was widespread free fluid in perihepatic and perisplenic areas. IV-contrasted abdominal computerized tomography (CT) revealed an unruptured saccular aneurysm in the left iliac artery, extravasation in the upper pole of the spleen, sub-capsular hematoma in the spleen, and widespread hemorrhagic fluid in the abdomen. The patient was diagnosed with rupture of the spleen and operated. It should be considered that patients applying to emergency services with abdominal pain and distension, with no trauma history, and anemia with no known cause in their examinations may have SSR.

Keywords: Spleen rupture, Spontaneous, Abdominal pain

Introduction

The spontaneous rupture of the spleen, which is the most injured organ in blunt abdominal traumas, is a rare cause of acute abdomen. Since the bleeding is rapid, it causes widespread intra-abdominal hemorrhage, threatens life, and mostly develops due to neoplastic and infectious causes [1,2]. Acute Myeloid Leukemia (AML) is a clonal disease characterized by proliferation and accumulation of the myeloid precursor cells in bone marrow, resulting in hematopoietic insufficiency. It is the most common type of leukemia in adults [3]. In this case report, a patient referring to the emergency service with the complaints of abdominal pain, nausea, vomiting, and a history of AML, who was diagnosed with spontaneous rupture of the spleen was discussed together with literature data.

Case presentation

Verbal consent of the patient was obtained while preparing this case report. A 62-year-old male patient was admitted to the emergency service with abdominal pain, nausea, vomiting, and diarrhea complaints that started the day before. When the patient arrived, his general condition was moderate, he was conscious and cooperative. The arterial blood pressure was 100/60 mmHg, pulse was 100 /min, body temperature was 36.4°C, and respiratory rate was 22/min. He had received chemotherapy for AML 3 years ago and recovered without any complications after the treatment. In his physical examination, there was widespread sensitivity in the abdomen mostly in the upper left quadrant, the abdomen seemed tense, and there was no defense or rebound. Rectal digital examination, as well as other system examinations, were normal. The patient was taken under observation, intravenous (IV) fluid replacement was administered, and the bladder was catheterized. In the blood tests, Blood Urea Nitrogen (BUN) was 31mg/dl (range 0-20mg/dl), creatinine was 1.9 mg/dl (range 0.67-1.17), C-reactive protein (CRP) was 27.8mg/L (range 0-5), and other biochemical parameters, Prothrombin Time (PT), Activated Partial Thromboplastin Time (aPTT) and electrolyte values were within normal range. His leukocyte count was 9630/mm^3 (range 3980-10200/mm3), platelet count was 99x10^3/uL (range 142-424), and hemoglobin was 7.7g/dl (range 14.1-18.1). FAST USG showed widespread free fluid in perihepatic and perisplenic areas. In the IV-contrasted abdominal computerized tomography (CT), there was an unruptured saccular aneurysm in the left iliac artery, extravasation in the upper pole of the spleen, sub-capsular hematoma in the spleen, and widespread hemorrhagic fluid in the abdomen (Figure 1). In clinical follow-up, arterial blood pressure dropped steadily, and the patient, who became anuric, was diagnosed with rupture of the spleen, and operated.

Figure 1: Transverse image compatible with spleen rupture and hematoma-coronal section-transverse image of unruptured saccular aneurism in the left iliac artery.
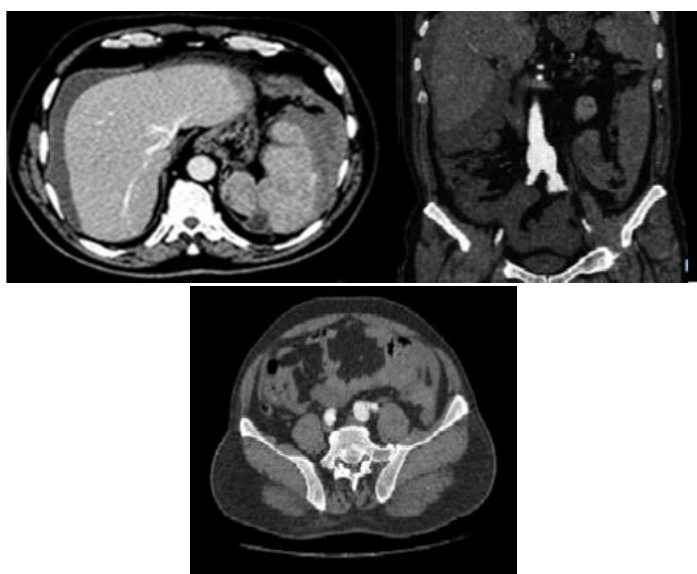
Discussion

Spontaneous Spleen Rupture (SSR) has a high mortality rate, and various factors have been blamed in its etiology. Hematological diseases, such as Non-Hodgkin Lymphoma, myeloproliferative disorders, and Acute Myeloid Leukemia, which are the most common hematological malignancies among neoplastic causes, are among them [1]. Hematological malignancies cause splenomegaly, which facilitates SDR due to distension or extra-medullary hematopoiesis by causing changes in the histological structure following the infiltration of the spleen. Coagulation disorders, on the other hand, cause spontaneous spleen rupture because of splenic infarctions and sub-capsular hemorrhage [4]. Low platelet count is also among the causes of hemorrhage [5]. The anamnesis of the patient showed AML that resulted in complete healing, and the patient had thrombocytopenia in past examinations. Aneurysm was observed in the left iliac artery in abdominal CT; however, no infarctions or any structural vascular pathologies that could cause hemorrhage in the spleen were detected. The patient had two possible etiologic factors for SSR: Previous AML could have infiltrated the spleen and prepared the ground for SSR, or it might have developed due to the hemorrhage caused by thrombocytopenia. It may also have developed idiopathically.

The main symptoms and findings of SSR are abdominal pain mostly felt in the left quadrant, pain spreading to the left shoulder (i.e., Kehr finding), nausea and vomiting. However, defense and rebound are generally not expected. Additional symptoms depend on the etiological causes. Dizziness, tachycardia, hypotension, and shock symptoms can be observed due to hemorrhage [6]. Our patient had abdominal pain, nausea, vomiting complaints, and widespread abdomen sensitivity and distension mostly in the upper left quadrant in physical examination, and no defense or rebound. The clinical symptoms and findings of our patient, who was in the pre-shock phase, were in line with the literature.

The diagnosis of SSR is made based on clinical symptoms and supportive imaging modalities. Parasynthesis is also an effective diagnostic method; however, negative results cannot rule out hemorrhage definitively [7, 8]. Today, the use of this method has decreased because it is an invasive method, takes time, and cannot definitively rule out intra-abdominal hemorrhage. The FAST USG is an inexpensive and practical method for fast diagnosis of intraperitoneal fluid accumulation or hematoma, which can be carried out at the bedside in the emergency service. Abdominal CT, on the other hand, clearly shows the severity of spleen damage and the degree of intraperitoneal hemorrhage and is preferred for hemodynamically stable patients. For hemodynamically unstable patients, the FAST USG is preferred as a fast and non-invasive diagnostic imaging method [9, 10]. We performed FAST USG at bedside to support clinical symptoms and detected intra-abdominal free fluid. Then, abdominal CT was performed to determine the severity of the damage. Since the prognosis is poor, the treatment of choice in SSR is splenectomy [11]. In line with the literature, the patient was urgently operated, and splenectomy was performed.

Conclusion

It should be considered that patients admitting to the Emergency Department with abdominal pain and distension, no history of trauma, and anemia with no known cause may have SSR. It should not be ignored that SSR may develop due to non-traumatic causes or idiopathically.

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Acute bilateral paramedian thalamic infarct in the differential diagnosis of hyperactive delirium: A case report

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Abstract

Acute bilateral paramedian thalamic infarct is a rare condition. Changes in consciousness, hypersomnia, mood disorders, cognitive problems and paralysis of vertical gaze may be observed in patients with acute bilateral paramedian thalamic infarct. Although it may have many causes, the most common is atherosclerotic small vessel disease. Some patients, who present with isolated neuro-psychiatric symptoms, may be misdiagnosed with a psychiatric illness. We herein present a patient presenting with the clinical features of hyperactive delirium who was diagnosed with acute bilateral paramedian ischemia. A 53-year-old female patient was admitted with complaints of changes in consciousness, agitation, and impairments in attention and memory, starting 2 days earlier and fluctuating during the day. Her history revealed hypertension and obesity. Levels of serum total cholesterol, high density lipoprotein (LDL) cholesterol and triglyceride were high, and the cardiac evaluation was within normal limits. Acute paramedian thalamic ischemia was detected through neuroimaging. Thalamic infarcts display different clinical features according to the localization of the lesions. Although many neurological and neuropsychological symptoms may be seen, thalamic infarcts may also present with psychiatric symptoms alone. Therefore, thalamic lesions should also be considered in acute or subacute behavioral changes in patients with no history of psychiatric disorders.

Keywords: Behavioral changes, Delirium, Paramedian thalamic ischemia

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Introduction

An oval-shaped mass of gray matter ideally situated at the core of the diencephalon, the thalamus conducts afferent impulses from the peripheral sensory receptors and transmits those from the cerebellum and basal ganglia to the motor cortex. There are many nuclei in the structure of the thalamus [1]. The medial and lateral geniculate nuclei play a role in visual and auditory functions, the pulvinar and lateral dorsomedial nuclei, in visual functions, the ventral posterolateral and posteromedial nuclei, in somatosensory functions, ventrolateral and ventroanterior nuclei, in motor functions, and medial dorsomedial nuclei, in autonomic and behavioral functions (2). In addition, the thalamus is involved in consciousness, sleep and paying attention. Vascular lesions of the thalamus can progress with different symptoms depending on the affected nucleus [1, 2].

The thalamus is fed by four major arteries, the tuberothalamic, inferolateral, paramedian and posterior choroidal arteries. Of these, bilateral infarct of the paramedian artery can cause confusion, hypersomnolence and changes in consciousness [3]. The etiology of bilateral thalamic infarct varies, and the main reason is small vascular disease developing because of atherosclerosis and cardiac embolism. In addition, thalamic infarcts are responsible for artery-to-artery embolisms due to large vessel atherosclerosis and constitute the etiology in migrainous stroke [2]. In the present report, a patient with acute bilateral paramedian thalamic ischemia with hyperactive delirium is presented.

Case presentation

The patient signed the informed consent form for sharing her details and images for scientific purposes. A 53-year-old female patient presented with complaints of impaired recognition of surroundings, agitation and visual hallucination commencing suddenly around 3:00 am two days earlier. During this period, the patient could not recognize her spouse as well. However, the patient had partially stabilized when she woke up in the morning. The complaints recurred during the day with fluctuating symptoms. She especially claimed that she was with dead friends and relatives and saw such acquaintances in her daily life. The patient's sleep-wake cycle was impaired, and she suffered from insomnia. The patient was first admitted to the psychiatry outpatient clinic with these complaints, and later referred to the neurology outpatient clinic with a pre-diagnosis of hyperactive delirium due to the organic factors. Her history revealed that she had hypertension, for which she used ramipril 5 mg 1x1, and had been smoking 10 cigarettes per day over 20 years. The patient's body mass index (BMI) was 34.75 kg/m^2. BMI was calculated as weight in kilograms (kg) divided by height in meters (m) squared (kg/m^2). Neurological examination revealed that she was confused. The patient followed commands although place and time orientation were impaired. The patient's speech was rapid without dysarthria. In memory examination, her records were preserved while recall was impaired. Long-term memory was within normal limits with impaired attention and concentration. No cranial nerve deficits were found, and cerebellar tests were normal. She had no Babinski sign, and deep tendon reflexes were bilaterally normoactive.

The laboratory examinations were as follows: Leukocyte count: 7.44 10^3/mm^3 (4.99–12.68), hemoglobin: 12.8 g/dL (11.9–14.6), platelet count: 159x10^3/mm^3 (150-450), international correction rate (INR): 1.0 (0.8–1.2), glucose: 101 mg/dL (74–106), urea: 39 mg/dL (17–43), creatinine: 1.04 mg/dL (0.66–1.09), aspartate aminotransferase (AST): 18 U/L (0–35) and alanine aminotransferase (ALT): 12 U/L (0–35), serum total cholesterol: 287 mg/dL (0-200), triglyceride: 218 mg/dL (0-150), high-density lipoprotein (HDL): 46 mg/dL (40-60) and low-density lipoprotein (LDL): 180 mg/dL (70-130). The electrolytes, thyroid hormones, and blood gas values, along with serum copper and ceruloplasmin levels were normal. No intracerebral hemorrhage was detected on brain computed tomography (CT). In diffusion-weighted magnetic resonance imaging (MRI), while hyperintense areas were seen in the paramedian areas of the bilateral thalamus, a hypointensity was detected in the apparent diffusion coefficient (ADC) map (Figures 1A, 1B). No flow limitations suggesting venous occlusions were determined on cerebral MRI venography, and the electroencephalography (EEG) examination was normal (Figure 2A, 2B, 2C).

Considering current findings, an acute ischemic stroke was considered in the patient. The blood pressure (BP) was measured as 140/100 mmHg. On transthoracic and transesophageal echocardiography (echo), the left ventricular diameters and wall movements were normal, and there was no thrombus. The ejection fraction (EF) was 52% (>50%), and no

arrhythmia was detected on 72-hour Holter electrocardiography (ECG). The carotid and vertebral artery examination with Doppler ultrasonography (USG) revealed an increased intimal-medial thickness in both Carotis Communis arteries (CCA). A 5x2 mm non-stenotic echogenic plaque was observed in the posterior wall of the right internal carotid artery (ICA). No stenosis was detected in vascular structures. Therefore, the metabolic, hematological, and genetic risk factors suggesting or leading to thrombocytosis were ruled out. The patient was administered olanzapine 10 mg/day and acetylsalicylic acid (ASA) 100 mg/day. On the 10th day of the treatment, orientation, and hallucination complaints, as well as insomnia began to improve. The patient was discharged with good health on the 17th day of treatment.

Figure 1: A) Hyperintensity in paramedian areas in bilateral thalamus on diffusion-weighted magnetic resonance imaging (MRI), B) Hypointensity in the same area on apparent diffusion coefficient (ADC) map
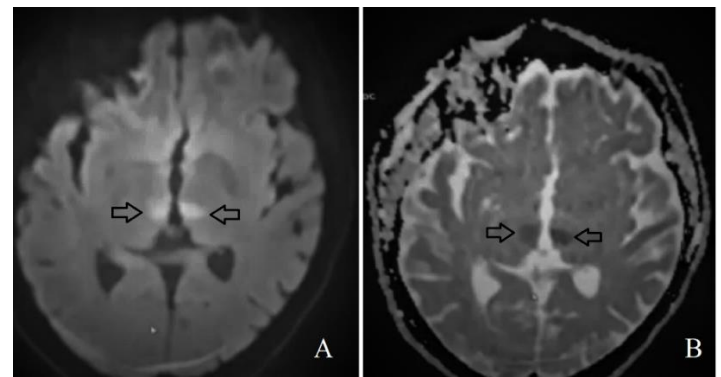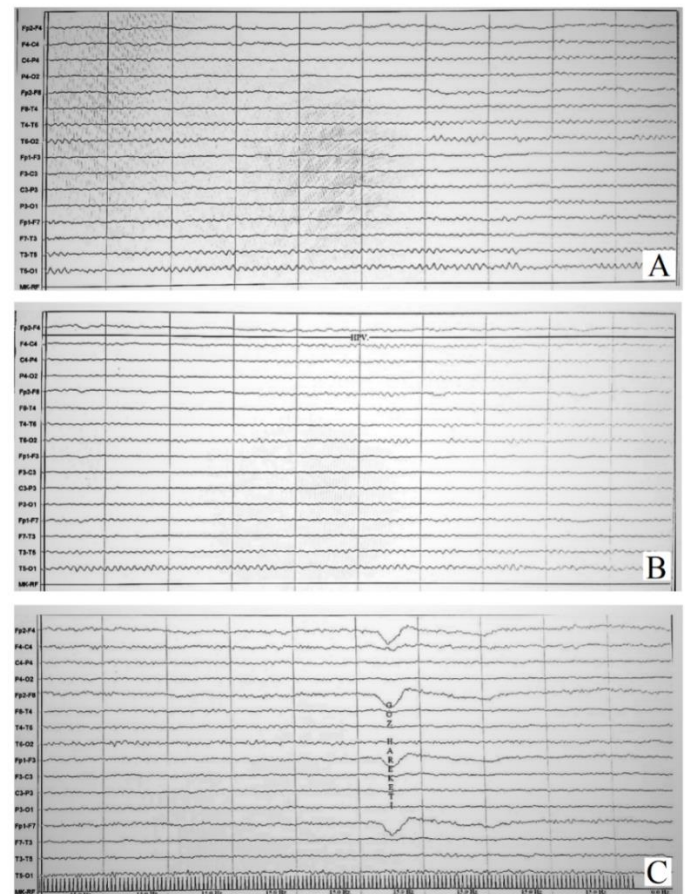

Figure 2: Electroencephalogram (EEG) A) Eyes opened, B) Hyperventilation, C) Intermittent photic stimulation (IPS): Electroencephalography findings consistent with normal bioelectrical activity

Discussion

Bilateral thalamic ischemia is an extremely rare entity and accounts for approximately 22-35% of all thalamic strokes. Atherosclerosis and cardioembolism are the most common etiological risk factors in bilateral thalamic strokes. Among other risk factors are atrial fibrillation, ventricular aneurysms, right-to-left shunts, left ventricular dysfunction and hypercoagulability [4]. Metabolic and toxic processes, infections and neoplasms can also mimic thalamic ischemia. Wernicke's encephalopathy occurs due to B1 (thiamine) deficiency, especially in patients with malabsorption. It presents with ataxia, changes in consciousness, antegrade amnesia and ocular dysfunction. The condition is especially seen among chronic alcohol users. On MRI, bilateral thalamic lesions, periaqueductal gray matter, tectum, mammillary bodies, and signal changes around the third ventricle are encountered [5]. Bilateral thalamic lesions may also be observed in the patients with central pontine myelinolysis, chronic kidney disease (CKD), liver disease, syndrome of inappropriate antidiuretic hormone secretion and diabetes mellitus (DM). Spastic hemiparesis, disorders of consciousness and pseudo-bulbar palsy are clinically observed with bilateral thalamic lesions [4, 5]. Diffusion restriction may be seen in the thalamus in Wilson's disease. Clinical symptoms, especially dysarthria, dystonia, ataxia, Parkinsonism, and psychiatric symptoms are often detected in young adults. Wilson's disease may also be accompanied by globus pallidus (GP), putamen and caudate nucleus lesions [6]. Creutzfeldt-Jakob disease is a neurodegenerative disease that can present with rapidly progressing dementia, ataxia, and myoclonus. In Creutzfeldt-Jakob disease, signal changes are observed in the putamen, caudate nucleus, and periaqueductal areas, in addition to the bilateral thalamic lesions [5, 6]. Bilateral thalamic glioma may also be encountered with similar MRI images and sometimes result in hydrocephalus. Patients with bilateral thalamic glioma are admitted to health facilities with personality changes or symptoms of dementia, they affect children or young adults, and their prognosis is poor since the lesions are deeply localized [5]. Bilateral thalamic lesions should be evaluated meticulously in differential diagnosis. The clinical findings in our patient had begun hyperacutely, and there was no alcohol use, history of malabsorption and chronic disease. The patient's current clinical, neurological, serological, and radiological findings prevented us from considering other differential diagnoses. In light of these findings, ischemic vascular disease was considered in our patient on the basis of atherosclerosis.

After strokes, delirium is quite frequent. However, stroke patients presenting with delirium are observed more rarely. The rate of delirium after a stroke was reported as 14.8%. Especially after acute ischemia affecting the left cortical and left subcortical areas, delirium develops at a higher rate. While left cortical ischemia was observed in 50% of stroke patients developing delirium, left subcortical ischemia was seen in 55.3%. No association was detected between brain stem and cerebellum involvement [7]. The thalamus, fusiform cortex, posterior parietal cortex, basal ganglion, and prefrontal cortex are the prominent brain regions related to emotions and memory. Emotional and memory disorders increase the risk of developing delirium by misinterpretation of the surrounding circumstances.

In the literature, no difference was reported in terms of hypoactive or hyperactive delirium development and stroke localization [8]. However, acute bilateral paramedian thalamic ischemia was detected in our patient who was admitted with hyperactive delirium.

Although bilateral paramedian thalamic ischemia can be diagnosed through MRI, they are often diagnosed by means of clinical findings. Especially sensorial changes, paralysis of vertical gaze, and memory impairments are observed in patients with bilateral paramedian thalamic ischemia. Dysarthria, changes in consciousness and posterior cerebral circulation in motor paresis should suggest ischemia. In some patients, severe cognitive impairment, amnestic syndrome, and executive dysfunction may be seen even a few months after the stroke. Inappropriate behaviors, apathy, and mood swings may also occur in patients with delirium [9, 10]. Cases of delirium associated with bilateral paramedian ischemia are extremely rare [11]. Fluctuations of consciousness, hallucination and agitation suggested hyperactive delirium in our patient. With the combination of olanzapine and antiaggregant therapy, the patient's symptoms subsided within a short time.

Conclusion

Bilateral paramedian ischemia is a rare condition, and there are many mimicking disorders. Although cognitive and ocular problems are commonly observed in patients with bilateral paramedian ischemia, delirium is rare. Bilateral paramedian thalamic ischemia should be considered in the differential diagnoses in case of acute delirium, especially in those without any history of previous psychiatric disorders.

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