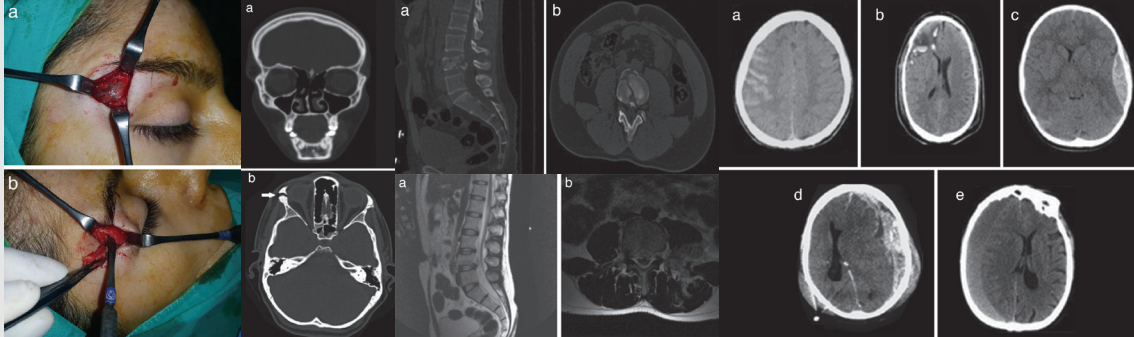


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Editor(s) as Author: Huizing EH, de Groot JAM, editors. *Functional reconstructive nasal surgery*. Stuttgart-New York: Thieme;2003.

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Evaluation of Maternal and Neonatal Outcomes in Cesarean Sections Performed in the Second Stage of Labor

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Abstract

Objective: To compare maternal and neonatal outcomes in cesarean deliveries in the first and second stage of labor.

Methods: Sixty-five patients who had caesarean section in the second stage of labor and 90 patients who had caesarean section in the first stage of labor were compared in terms of maternal and neonatal complications. Patient data was obtained from patient files and hospital electronic system records.

Results: Of the 155 patients included in the study, 58.1% (n=90) had a cesarean section in the first stage of labor and 41.9% (n=65) in the second stage of labor. The incidence of intraoperative surgical complication and postoperative endomyometritis was significantly higher in the cesarean section in the second stage of labor compared to the cesarean section in the first stage of labor. There was no significant difference in terms of blood transfusion requirement and neonatal complications between two groups.

Conclusion: Maternal morbidity risk is significantly higher in cesarean sections performed in the second stage of labor than in the first stage of labor.

Keywords: Cesarean section, maternal outcomes, neonatal outcomes, second phase of the labor

INTRODUCTION

The rate of caesarean section in the world is increasing and it has reached 50% today (1). In our country, this ratio was around 6% between 1983-2001 and now it has increased up to 30% (2). The World Health Organization (WHO) reports that the cesarean birth rate should be less than 15% (3). Maternal mortality was reported to be 6/100000 in vaginal delivery and 28/100000 in cesarean delivery in healthy pregnant women without medical and obstetric problems (4). Maternal morbidities are also higher in cesarean deliveries than vaginal deliveries. Complications such as postpartum febrile morbidity, deep vein thrombosis, need for blood transfusion, long hospital stay, organ injuries, intraabdominal adhesions, infertility and chronic pelvic pain are also more frequent in cesarean delivery (5).

Van Ham et al. (6) and Nielsen et al. (7) reported intraoperative surgical complication rates as 11.6% and 14.8% in cesarean deliveries. Regular uterine contractions, presence of membrane rupture, cervical patency more than 3 cm, and engagement are the most important risk factors for intraoperative complication development (7-9). In this study, 155 term primary cesarean section patients were divided into two groups as cesarean section in the “first” and “second” stages of labor, and age, gravida, parity, gestational week, caesarean indication, hospital stay, blood transfusion requirement, maternal outcomes such as intraoperative and postoperative surgical complications, and neonatal outcomes such as fetal birth weight, Apgar score and neonatal intensive care requirement were compared.



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METHODS

Istanbul Okmeydanı Training and Research Hospital Ethics Committee approved this study (no: 253, dated 23.12.2014). This study was performed by examining the records of cesarean section patients at the Obstetrics and Gynecology Clinic of Okmeydanı Training and Research Hospital between 2010 and 2014. Sixty-five patients who had caesarean section in the second stage of labor and 90 patients who had caserean section in the first stage of labor were compared in terms of maternal and neonatal complications. Patients with maternal diseases (hypertension, heart disease, diabetes mellitus, etc.) and those with fetal anomalies were not included in the study group.

Statistical Analysis

The statistical analysis was performed using Number Cruncher Statistical System (NCSS) 2007 program.

RESULTS

The maternal and fetal characteristics of the patients included in the study are presented in Table 1. The mean age of the patients was 27.52±6.42 years (18-40 years), mean gravida was 2.17±1.43 (1-8), mean parity was 0.90±1.21 (0-5), and mean gestational age was 38.32±0.91 weeks (37-40 weeks). The mean length of hospital stay was 2.58±0.78 days (2-7 days). The mean birth weight was 3449.43±403.44 grams (2470-4560 grams). The mean 1-minute and 5-minute Apgar scores were 7.88±0.72 (3-9) and 8.23±0.82 (7-9). Fifty-eight point one percent (n=90) of the cesarean sections occurred in the first stage and 41.9% (n=65) occurred in the second stage of labor.

	Min-max	Mean ± SD	
Age, years	18-40	27.52±6.42	
Gravida	1-8	2.17±1.43	
Parity	0-5	0.90±1.21	
Weeks of pregnancy	37-40	38.32±0.91	
Length of hospital stay (days)	2-7	2.58±0.78	
Birth weight (gr)	2470-4560	3449.43±403.44	
1-minute Apgar	3-9	7.88±0.72	
5-minute Apgar	4-9	8.23±0.82	
		n	%
Birth weight	<4000 gr	138	89
	≥4000 gr	17	11
Birth stage	1 st stage	65	41.9
	2 nd stage	90	58.1
Min: Minimum, Max: Maximum, SD: Standard deviation			

Findings related to maternal and fetal mortality and morbidity after cesarean section are presented in Table 2. Maternal complications were as follows: blood transfusion in 25 patients, B-Lynch sutures due to atony hemorrhage in one patient, T-shape incision in one patient, hematoma in two patients, extended incision in nine patients, bladder injury in two patients and postpartum endometritis in 18 patients. Neonatal complications included need for intensive care in 23 newborns and 2 neonatal deaths.

The cesarean indications are given in Table 3.

There was no statistically significant difference between the two groups in terms of age, gravida, parity, gestational week, hospital stay, 1-minute and 5-minute Apgar scores and birth weight (p>0.05) (Table 4).

Surgical complications and postpartum endometritis were found to be higher in cesarean sections in the second stage of labor (p=0.06; p<0.01). The difference between two groups in terms of neonatal intensive care need, neonatal mortality and maternal blood transfusion rates was not statistically significant (p>0.05) (Table 5).

The indications of the patients who had cesarean section in the first stage of labor were fetal distress, cephalopelvic disproportion (CPD) and obstructed labor, respectively. The indications of the patients who had cesarean section in the second stage of labor were CPD, obstructed labor and fetal distress, respectively (Table 6).

	n	%
Blood transfusion	No	130
	Yes	25
Surgical complication	No	140
	Yes	15
B-Lynch suture	1	6.7
Hematoma	2	13.3
Extended incision	9	60.0
Bladder injury	2	13.3
T-shape incision	1	6.7
Postpartum hysterectomy	-	-
Postpartum endometritis	18	11.6
Maternal mortality	-	-
Need for neonatal intensive care	23	14.8
Neonatal mortality	2	1.3

DISCUSSION

In the United States, the cesarean section rate of 2% was under discussion in 1958, whereas it was increased to 24.1% in 1986 (10). Although there has been a decrease in cesarean rates in the 1990s due to the increase in maternal morbidity and increase in operating costs with no change in infant mortality, the rate of caesarean section in USA is approximately 22% (10). According to the data of the Ministry of Health in Turkey, the rate of caesarean section was 14% in 1998 and it was reported as 50.4% in 2013. In the retrospective studies conducted in our country, the rate of caesarean section varies between 18% and 33% (11-13).

The main reason for the increase in cesarean section rates is the expansion of indication groups, including previous cesarean section, CPD, breech presentation, fetal distress and obstructed labor. In addition, elective caesarean section preferences have increased because of the thought of less pain, less harm to the pelvic organs and more benefits for the fetus (14). Increased cesarean indications increase recurrent cesarean section cases. The most common caesarean section indication in our country is recurrent cesarean section and the rate is 30% (15).

In many clinics, fetal distress indication is performed by fetal electronic monitoring. This method has a high false positive rate and intrapartum fetal monitoring application

Table 3. Findings related to cesarean indications

	n	%
CPD	49	31.6
Fetal distress	34	21.9
Obstructed labor	30	19.4
Dense meconium	13	8.4
Breech presentation	10	6.5
Other indications (HPV, large baby etc.)	39	25.2
Anhydramnios	6	3.87
Placental detachment	4	2.58
Previous lumbar surgery	1	0.65
HPV	5	3.23
Precious pregnancy	1	0.65
Cord prolapse	3	1.94
Chorioamnionitis	1	0.65
Macrosomia	9	5.81
Meconium + large baby	1	0.65
Transverse presentation	4	2.58
Umbilical hernia surgery	1	0.65
Incompatible patient	2	1.29
Face presentation	1	0.65

CPD: Cephalopelvic disproportion, HPV: Human papillomavirus

also contributes to the increase in cesarean rate (15, 16). In a Cochrane database review, the authors reported that fetal

Table 4. Evaluation of maternal and fetal properties with birth stage of cesarean section

		Birth stage		p
		1 st stage (n=90)	2 nd stage (n=65)	
Age	Mean ± SD	28.04±6.57	26.80±6.19	a0.235
	Min-max (median)	18-40 (28)	18-40 (27)	
Gravida	Mean ± SD	2.19±1.53	2.15±1.30	b0.693
	Min-max (median)	1-8 (1.50)	1-6 (2)	
Parity	Mean ± SD	0.94±1.29	0.85±1.10	b0.973
	Min-max (median)	0-5 (0)	0-4 (0)	
Weeks of pregnancy	Mean ± SD	38.33±0.93	38.29±0.89	b0.793
	Min-max (median)	37-40 (38)	37-40 (38)	
Length of hospital stay (days)	Mean ± SD	2.49±0.70	2.71±0.86	b0.057
	Min-max (median)	2-5 (2)	2-7 (3)	
1-minute Apgar	Mean ± SD	7.88±0.71	7.89±0.75	b0.742
	Min-max (median)	6-9 (8)	3-9 (8)	
5-minute Apgar	Mean ± SD	8.26±0.86	8.20±0.77	b0.321
	Min-max (median)	6-9 (8)	4-9 (8)	
Birth weight; n (%)	<4000 gr	82 (91.1)	56 (86.2)	c0.330
	>4000 gr	8 (8.9)	9 (13.8)	

SD: Standard deviation, Min: Minimum, Max: Maximum, aStudent's t-test, bMann-Whitney U test, cPearson chi-square test

Table 5. Evaluation of maternal and fetal outcomes with birth stage of cesarean section

		Birth stage		p
		1 st stage (n=90)	2 nd stage (n=65)	
Postpartum endometritis	No	85 (94.4)	52 (80.0)	a0.006**
	Yes	5 (5.6)	13 (20.0)	
Neonatal intensive care need	No	75 (83.3)	57 (87.7)	a0.451
	Yes	15 (26.7)	8 (12.3)	
Neonatal mortality	No	88 (97.8)	65 (100.0)	b0.510
	Yes	2 (2.2)	-	
Blood transfusion	No	78 (86.7)	52 (80.0)	a0.265
	Yes	12 (13.3)	13 (20.0)	
Surgical complication	No	86 (95.6)	54 (83.1)	a0.010**
	Yes	4 (4.4)	11 (16.9)	

aPearson chi-square test, bFisher's exact test, **p<0.01

monitoring increased the cesarean section frequency by 40%, but did not significantly reduce the incidence of admission and cerebral palsy in the neonatal intensive care unit (17). In our study, fetal distress indication was in second place among the indications for primary cesarean sections with a rate of 21.9%. This rate is reported to be 21.6% at Şişli Etfal Hospital (18), 16.3% in Obstetrics and Gynecology Clinic of Dicle University Faculty of Medicine (19) and 19.1% in Obstetrics and Gynecology Clinic of Yüzüncü Yıl University Faculty of Medicine (20). The primary cesarean section rate is 9.7% in the United States (21).

In a study in which 34995 cases were included, intrapartum fetal monitoring was evaluated and it was determined that more cesarean decisions were made in the group in which all pregnant women were monitored compared to the selective

monitorization group, but there was no difference in perinatal results (22). In our study, there was no statistically significant difference between the groups in terms of 5-minute Apgar score and need for neonatal intensive care unit.

In the studies, no cause-effect relationship was found between the increase in cesarean rates and the decrease in perinatal mortality and morbidity. It was reported that the factors affecting perinatal mortality are only the presentation of the fetus, maternal diseases leading to pregnancy complications, number of fetuses, ethnicity and maternal age (23). Respiratory distress syndrome type-II incidence rate in vaginal deliveries after 37th gestational week is 5.3, whereas this rate is 35.5% for cesarean sections not in labor and 12.2% for cesarean section in labor (24). In another study in neonates between 37-42 weeks of gestation, an increase was observed in all morbidities in cesarean sections not in labor compared to spontaneous, elective or induced vaginal deliveries. The ventilator requirement is 4.51 times, the asphyxia is 4.91 times, the sepsis is 1.40 times, and the intensive care unit stay was 1.98 times more (25). In our study, neonatal mortality rate was calculated as 14.8% and neonatal mortality rate was calculated as 1.3%. Need for neonatal intensive care unit and neonatal mortality were comparable between those with cesarean section in the 1st stage and those with cesarean section in the second stage of labor.

Although significant decrease in perinatal mortality and morbidity has been observed with widespread use of ultrasonography, it is a fact that this practice increases the cesarean rates. There is a 15% margin of error in the predicted fetal weight in the last trimester. Although the term “fetal macrosomia” varies according to the populations, the type of delivery also varies according to the maternal pelvis structure. Deciding on only the expected birth weight increases the cesarean rate. In our study, the rate of those who underwent cesarean with the indication of macrosomia was 1.94%. The reason for this low rate is that cesarean delivery due to this indication is made without entering into the active stage.

CPD causes prolongation of labor, physical and psychological fatigue of the mother, fetus to remain under stress or even traumatization, varying degrees of damage to the birth canal and more workload and concern to the person who follows the birth. Therefore, nowadays, the people who are interested in birth seek to predict CPD and find a treatment without delay to prevent any harm to the mother or the fetus. CPD cannot always be predicted and cesarean section with CPD diagnosis is increasing (26). CPD indication rate among patients who underwent cesarean section was reported as 5.6% by Yumru et al., (15) and 7.3% by Kara (27). In a study conducted in a university hospital in Senegal, CPD was

Table 6. Evaluation of indications according to birth stage of cesarean section

		Birth stage		p
		1 st stage (n=90)	2 nd stage (n=65)	
CPD	No	71 (78.9)	35 (53.8)	a0.001**
	Yes	19 (21.1)	30 (46.2)	
Fetal distress	No	68 (75.6)	53 (81.5)	a0.374
	Yes	22 (24.4)	12 (18.5)	
Obstructed labor	No	74 (82.2)	51 (78.5)	a0.559
	Yes	16 (17.8)	14 (21.5)	
Dense meconium	No	81 (90.0)	61 (93.8)	a0.394
	Yes	9 (10.0)	4 (6.2)	
Breech presentation	No	84 (93.3)	61 (93.8)	b1.000
	Yes	6 (6.7)	4 (6.2)	
Other indications (HPV, large baby etc.)	No	59 (65.6)	57 (87.7)	a0.002**
	Yes	31 (34.4)	8 (12.3)	
Anhydramnios		6	0	
Placental detachment		3	1	
Previous lumbar surgery		1	0	
HPV		4	1	
Precious pregnancy		1	0	
Cord prolapse		2	1	
Chorioamnionitis		1	0	
Macrosomia		6	3	
Meconium + large baby		0	1	
Transverse presentation		4	0	
Umbilical hernia surgery		1	0	
Incompatible patient		2	0	
Face presentation		0	1	

CPD: Cephalopelvic disproportion, HPV: Human papillomavirus
^aPearson chi-square test, ^bFisher's exact test, **p<0.01

the leading cause of caesarean section with a rate of 31% (28). In our study, the rate of caesarean section with CPD indication was the leading cause with a rate of 31.6%. The reason for this is that the patients included in the study were selected from caesarean section cases after the beginning of active labor. The reason for increased CPD in the second stage of labor is the avoidance from labor with intervention (vacuum-forceps).

In a WHO report published in 2002, maternal mortality due to caesarean section was reported to be 41/100.000 in the United States and 160-220/100,000 in developing countries (29). The WHO perinatal health-related questionnaire showed that caesarean delivery increased the need for postpartum antibiotic use and maternal blood transfusion, but caused no significant reduction in maternal morbidity and mortality (30). Operative complications are more common in emergency cases than in elective cases (31). In our study, the rate of surgical complication in patients undergoing caesarean section in the first stage of labor was 4.4% and in patients in the second stage was 16.9%.

In their study, Bagratee et al., (32) suggested that prophylactic antibiotic use in caesarean operations did not reduce postpartum complication rates such as febrile morbidity, wound infection, endometritis, pneumonia and postoperative infection morbidity. In contrast, Killian et al., (33) reported that less infection rates were detected in patients who received antibiotics in their study. Smiill and Hofmery (34) reported less frequent endometritis, wound infection and urinary infection in antibiotic users. In a study by Ehrenkranz et al., (35), the rate of infection in caesarean deliveries was found to be 0.9% for those who received antibiotic prophylaxis and 3.7% for those who did not. In our study, the postpartum endometritis rate was also found to be 11.6%. Endometritis rate was found to be 5.6% in the first stage of labor and 20% in the second stage.

Lydon-Rochelle et al., (36) stated that caesarean delivery increases the risk of endometritis, wound infection and thromboembolism, and therefore, the length of hospital stay increases due to these complications. In our study, the mean hospital stay was 2.58 days, with a mean of 2.49 days in the first stage of labor and 2.71 days in the second stage of labor.

Haas et al., (37) noted that the most common intraoperative complication in caesarean delivery was uterocervical laceration and associated blood loss. In our study, intraoperative uterocervical laceration rate was 9.7%. This rate was 4.4% for caesarean section in the first stage of labor and 16.9% for caesarean section in the second stage.

CONCLUSION

Maternal morbidities such as intraoperative uterocervical laceration and postpartum endometritis, which may increase the need for blood transfusions in caesarean section performed in the second stage of labor, are significantly higher in the 2nd stage of labor. Therefore, in the presence of the necessary conditions, intervention (vacuum-forceps) delivery in the second stage of labor should be considered as an alternative to caesarean delivery. It may be encouraging to provide appropriate working conditions and environment that will allow physicians to make decisions based on obstetric conditions, away from legal concerns.

Ethics

Ethics Committee Approval: Istanbul Okmeydanı Training and Research Hospital Ethics Committee approved this study (no: 253, dated 23.12.2014).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.D.Y.Y., V.M., B.C., G.P., A.P., Concept: F.D.Y.Y., Design: F.D.Y.Y., V.M., Data Collection or Processing: F.D.Y.Y., .M., B.C., G.P., A.P., Analysis or Interpretation: F.D.Y.Y., B.A., Literature Search: F.D.Y.Y., B.A., Writing: B.A.

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Comparison of Nutritional Status with Clinical Status, Laboratory Results and NRS-2002 Score in Patients Requiring Nutritional Support

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Abstract

Objective: It is known that treatment is more difficult, and morbidity and mortality increases in cases where nutritional support is required. Nutritional risk screening-2002 (NRS) score and the presence of malnutrition were investigated in patients who were consulted to our nutritional support team and the relationship between this scoring and clinical course was investigated. 2002 and the presence of malnutrition were investigated in patients who were consulted to our nutritional support team and the relationship between this scoring and clinical course was investigated.

Methods: The patients who were consulted to nutrition support team between January 2013 and June 2016 were included in this retrospective study. Patients with and without malnutrition according to NRS-2002 were compared in terms of age, gender, primary disease, body mass index (BMI), calorie need, albumin, prealbumin, C-reactive protein and the length of hospital stay.

Results: A total of 450 cases were included in the study. There was a significant difference in terms of age, BMI, albumin value and mortality among cases with and without malnutrition. Mortality was not observed in the cases without malnutrition, and one out of five cases with malnutrition was found to die. According to the correlation analysis, it was observed that malnutrition score increased as age increased, and that malnutrition score decreased as BMI, calorie need and albumin values increased. There was no difference between two groups in terms of gender, diagnosis, prealbumin, C-reactive protein and length of hospital stay.

Conclusion: Our study emphasized the importance of absolute review of body mass index, albumin and C-reactive protein levels in order to evaluate malnutrition more effectively in patients with malnutrition according to NRS-2002. We think that it is important to monitor the patients closely by establishing nutritional support units in hospitals, especially in the neurology and oncology clinics, since the detection of malnutrition and nutritional support affects the clinical course.

Keywords: Albumin, nutrition, malnutrition

INTRODUCTION

Malnutrition is quite high (20-40%) in hospitalized patients. Its prevalence depends on the assessment of underlying nutritional difficulties and clinical evaluation parameters (1, 2). It is

known that treatment is more difficult and morbidity-mortality increases in cases requiring nutritional support (3, 4). Although various assessment methods and indicators (biochemical tests and anthropometric indices) are currently used in the



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assessment of nutritional status, there is no scale that is accepted as the gold standard (5). Malnutrition is critically important in hospitalized patients and is associated with poor wound healing, high risk of postoperative infection, decreased efficacy, and prolonged hospital stay (6). Some traditional approaches, such as body mass index (BMI), biochemical test and anthropometric measurements are used in the diagnosis of malnutrition, alone or in combination (5).

Nutritional risk screening-2002 (NRS) is a screening system developed by Kondrup et al. (7). It is suggested that the nutritional status is related to the severity of the disease. This scoring system includes several parameters such as weight loss, BMI and oral intake, presence of additional disease, age and general condition of the patient. It is also a recommended screening test for hospitalized patients by the European Society for Clinical Nutrition and Metabolism. In this screening system, 3 points or more indicate malnutrition. In many studies, NRS was used in the parameters used to determine the other nutritional status and was found to be more useful and more sensitive than the others. Albumin, prealbumin, C-reactive protein (CRP) and BMI are used to determine nutritional status. However, their use alone in determining nutritional status is controversial (8).

Objective

The presence of malnutrition was investigated by NRS-2002 in patients consulted to our nutrition support team, and the relationship between this scoring and clinical course was investigated. In addition, the relationships between NRS-2002 score of 3-7 and the variables such as age, gender, BMI, primary diagnosis, energy need, hospital stay after nutritional support and the patient's final condition will be investigated.

Hypothesis

There is relationship between albumin, prealbumin, CRP, age, gender and BMI between patients with and without malnutrition according to NRS.

METHODS

Our study was approved by the Ethics Committee of İzmir Bozyaka Training and Research Hospital, University of Health Sciences (no: 3, dated: 09.08.2016). This study was a retrospective cohort study and included 450 patients who were consulted to our nutritional support unit (NSU) with the diagnosis of malnutrition between January 2013 and June 2016. All subjects were included in the study. Dependent variables were determined as the NRS score and the patient's final status (discharge, transfer, death).

The independent variables were age, gender, primary disease of the patient (such as oncological, neurological, cardiovascular diseases, chronic renal failure, coronary artery diseases), mortality, biochemical parameters (albumin, prealbumin, CRP) which are related or assumed to be related to malnutrition, BMI, daily calorie need and length of hospital stay after nutritional supplementation.

Dependent Variables

NRS score: the NSU used the table suggested by Kondrup et al., (7) to calculate NRS-2002 score. According to the score, patients having a score ≥ 3 were classified as malnourished group and patients having a score < 3 were classified as well-nourished group.

Length of hospitalization: it was evaluated as the time from the consultation date to the final status of the patient.

Independent Variables

a) Variables related to the clinical situation Age, gender and primary diagnosis: the data were collected from the patient files and nutritional assessment forms. Primary diagnoses were grouped as oncological, neurological, cardiovascular diseases and other.

Mortality status: the patients who died during the hospitalization period were evaluated.

b) Variables related to nutritional status

BMI: BMI is the value calculated by dividing weight (kg) by the square of height in meters [Weight (kg)/height (m²)]. BMI values were grouped as follows: < 18.5 kg/m² as underweight, between 18.5-24.9 kg/m² as normal weight, between 25-29.9 kg/m² as overweight and ≥ 30 as obese.

Daily calorie need: It was calculated using Schofield formulas (9) and factors such as presence of infection, ventilation and fever were considered.

c) Biochemical parameters: albumin, prealbumin and CRP values were used in the initial evaluation by the NSU. The values within the three days following the onset of intervention were used for the patients with missing parameters in the initial evaluation. Cases without relevant tests were not included in the statistical analysis. The parameters were grouped as follows:

-Albumin: normal (above 3.5g/dL), low (2.5-3.4 g/dL) and very low (below 2.4 g/dL),

-Prealbumin: normal (above 20 mg/dL), low (20-12 mg/dL) and very low (below 11 mg/dL),

-CRP: normal (0-10 mg/L), high (11-50 mg/L) and very high (over 51 mg/L).

Statistical Analysis

IBM SPSS (Statistical Package for the Social Sciences) version 21.0 program was used for statistical analysis. Numerical variables are summarized with mean, standard deviation, minimum and maximum values. Categorical variables are expressed as numbers and percentages. The normality of numerical variables was examined by Kolmogorov-Smirnov test. Numerical variables were compared between two groups by Student's t-test or Mann-Whitney U test, where appropriate. The difference between three or more independent groups was evaluated by using one-way ANOVA or Kruskal-Wallis test, where appropriate. The relationship between numerical variables was investigated by Pearson or Spearman correlation coefficients. The significance level was taken as $p < 0.05$ in all statistical analyzes.

RESULTS

Regarding genders, 52.4% of the study group was male and 47.6% was female. Seventy one point five percent of patients with nutritional support were 65 years or older. Thirty-seven point two percent of the patients had neurological and 30.7% of the patients had oncological primary diagnoses. According to the BMI levels, 57.4% were normal. Regarding calorie distributions, it was determined that 48.7% of the calorie need was in the 1501-1800 range. According to the NRS score, 94.7% of the patients who were consulted to the NSU were malnourished and 5.3% of them were well-nourished. Albumin levels were very low in 50.5%, low in 37.9% and normal in 11.5%. When the prealbumin levels were examined, it was found to be very low in 90.5%. CRP levels of patients were 90% high or very high. It was found out that 19.8% of the cases were dead. Demographic data on the clinical and nutritional status of the cases are presented in detail in Table 1.

Data on age, height, weight, BMI, calorie need, NRS score, length of hospital stay, albumin, prealbumin, CRP values are given in Table 2. There was a significant difference between malnourished and well-nourished patients in terms of age, BMI, albumin and mortality ($p < 0.05$). Only 10.8% of the patients with malnutrition according to the NRS score and 23.8% of the patients without malnutrition were found to have normal albumin levels. It was determined that 84.3% of patients with malnutrition had normal weight and overweight. No mortality was observed in patients without malnutrition according to NRS. In patients with malnutrition according to NRS, mortality was found to be 20.9%.

In terms of other variables, there was no significant difference between malnourished and well-nourished groups ($p > 0.05$) (Table 3). Mean values of continuous variables in patients with and without malnutrition according to NRS score are shown in Table 4. The mean age of the patients with malnutrition was significantly higher than those without malnutrition. Albumin levels were lower in patients with malnutrition and CRP levels were higher in patients with malnutrition, and this difference was significant ($p < 0.05$).

It was observed that there was no significant difference between the patients' final status (death, discharge, transfer) in terms of

		n	%
Gender	Male	236	52.4%
	Female	214	47.6%
Age (years)	20-44	24	5.3%
	45-64	104	23.1%
	65-74	96	21.3%
	75-84	132	29.3%
	85+	94	20.9%
Diagnosis	Others (cardiac, renal failure, etc.)	130	29.0%
	Oncological	138	30.7%
	Cardiovascular	14	3.1%
	Neurological	167	37.2%
BMI	Underweight	67	15.3%
	Normal	252	57.4%
	Overweight	89	20.3%
	Obese	31	7.1%
Calorie requirement (kcal/day)	≤1200	34	7.6%
	1201-1500	118	26.2%
	1501-1800	219	48.7%
	1801-2100	73	16.2%
	≥2101	6	1.3%
According to NRS score	No malnutrition	24	5.3%
	Malnutrition	426	94.7%
Albumin (g/dL)	Very low	138	37.9%
	Low	184	50.5%
	Normal	42	11.5%
Prealbumin (g/dL)	Very low	153	90.5%
	Low	14	8.3%
	Normal	2	1.2%
CRP (mg/L)	Normal	36	10%
	High	207	56%
	Very high	125	34%

BMI: Body mass index, NRS: Nutrition risk screening, CRP: C-reactive protein

BMI levels ($p>0.05$). Regarding diagnosis, there was no significant difference between groups in mean calorie ($p>0.05$).

When the variables were correlated with the NRS score, there was a statistically significant linear relationship between age, albumin, BMI and calorie ($p<0.05$). A weak positive correlation was found between NRS score and age, whereas there was a weak negative correlation between albumin, BMI and calorie. The correlation between NRS score and the variables is given in detail in Table 5.

DISCUSSION

It is important to determine possible nutritional risk/malnutrition in hospitalized patients and this may affect morbidity and mortality (10). Nutrition has a significant impact on health and functional capacity. While the incidence of malnutrition is about 15% among healthy elderly people, protein energy malnutrition is a major problem in the elderly who are not healthy (11). This rate is up to 80% especially in hospitalized elderly patients (12). Malnutrition rates in hospitalized patients vary between 15% and 60%, depending on the type of hospital, the region of the hospital and the population of the study (13). In our study, consistent with the literature, the mean age of the patients was 71 and 71.5% were in the 65 years old group.

Patients with malnutrition are known to have higher mortality and morbidity rates, longer hospital stay, and more drug use than patients without malnutrition (14). In our study, there was

Table 2. Data on age, height, weight, BMI, calorie need, NRS, hospital stay, albumin, prealbumin and CRP values

	n	Minimum	Maximum	Mean	SD
Age (years)	450	20.00	101.00	71.73	15.16
Height (cm)	450	130	190	165.24	9.20
Weight (kg)	450	25	112	62.40	13.83
BMI	450	12.02	44.44	22.80	4.57
Calorie requirement (kcal/day)	450	900	2400	1632.66	244.37
NRS	450	1	7	4.24	1.23
Length of hospital stay (days)	450	0.00	98.00	12.64	13.66
Albumin (g/dL)	364	1.10	43.90	2.88	2.24
Prealbumin (g/dL)	169	1.00	34.00	11.87	5.90
CRP (mg/L)	368	0.20	361.00	87.00	73.51

SD: Standard deviation, BMI: Body mass index, NRS: Nutrition risk screening, CRP: C-reactive protein

no mortality in the well-nourished group and the mortality rate in the malnutrition group was very high with 20.9%.

None of the plasma proteins, such as albumin, pre-albumin, transferrin, retinol binding protein used in addition to other parameters, are not fully sensitive or specific alone in the assessment of nutritional status (11). However, albumin, prealbumin and CRP are investigated in many different ways such as the evaluation of nutritional status and determination of the prognosis of oncologic patient (15). Albumin is not practical for the evaluation of acute changes in nutritional status due to its long half life; however, it can give better results as a chronic malnutrition index (16). Transferrin is associated with

Table 3. Distribution and relationship of age, gender, diagnosis, BMI, albumin, CRP, prealbumin and mortality rates of patients with and without malnutrition according to NRS score

		NRS score				p
		No malnutrition		Malnutrition		
		n	%	n	%	
Gender	Male	11	45.8%	225	52.8%	0.505
	Female	13	54.2%	201	47.2%	
Age (years)	20-44	4	16.7%	20	4.7%	0.001*
	45-64	14	58.3%	90	21.1%	
	65-74	4	16.7%	92	21.6%	
	75-84	1	4.2%	131	30.8%	
	85+	1	4.2%	93	21.8%	
Diagnosis	Neurological	5	20.8%	162	38.1%	0.284
	Oncological	11	45.8%	127	29.9%	
	Cardiovascular	1	4.2%	13	3.1%	
	Others	7	29.2%	123	28.9%	
BMI	Underweight	2	8.3%	65	15.7%	0.022*
	Normal	9	37.5%	243	58.6%	
	Overweight	9	37.5%	80	19.3%	
	Obese	4	16.7%	27	6.5%	
Albumin (g/dL)	Very low	2	9.5%	136	39.7%	0.012*
	Low	14	66.7%	170	49.6%	
	Normal	5	23.8%	37	10.8%	
CRP (mg/L)	High	10	71.4%	197	61.9%	0.474
	Very high	4	28.6%	121	38.1%	
Prealbumin (g/dL)	Very low	4	80.0%	149	90.9%	0.397
	Low	1	20.0%	13	7.9%	
	Normal	0	0.0%	2	1.2%	
Death	Yes	0	0.0%	89	20.9%	0.007*
	No	24	100.0%	337	79.1%	

*: Chi-square test, BMI: Body mass index, NRS: Nutrition risk screening, CRP: C-reactive protein

iron status and is expected to decrease in nutritional deficiency by increasing the serum concentration of iron deficiency that may be associated with nutritional disorders. Therefore, the use for nutritional assessment is controversial (16). Similarly, in the presence of inflammation, the prealbumin value decreases and the CRP value increases. Correlation of CRP with malnutrition is a matter of debate (17). Prealbumin is a more sensitive nutrient evaluation marker than albumin due to its short half-life of 2 days (15). Ho et al., (18) suggest that low prealbumin levels are an independent risk factor in cancer patients and are used in terminal cancer patients. In our study, no relation was found between the malnutrition group and prealbumin. More studies are needed to clarify this issue.

In their study, Gibbs et al., (19) showed that the low pre-operative albumin value was an important indicator of poor clinical course. As albumin may be low in sepsis and inflammatory conditions, it is insufficient to assess the nutritional status with albumin alone (11). Although it is advocated that there is no relationship with nutrition because of its change with body composition, it is still in use in the presence of inflammation and weight loss. Albumin levels can also be used to determine the presence of cachexia (20). In contrast, different studies have shown the relationship with malnutrition (17, 21). In our study, albumin was significantly lower in the malnutrition group.

In the literature, it is stated that the length of hospital stay is longer in malnourished patients (6, 22). In our study, it was 12.8 and 9 days in the group with and without malnutrition, respectively. However, the difference was not statistically significant. The insignificance was thought to be due to smaller number of patients without malnutrition.

In our study, the correlation test between NRS score and age, albumin, prealbumin, CRP, BMI, length of hospital stay and calorie revealed a weak positive correlation between NRS score and age, and a weak negative correlation between albumin, BMI and calorie. In other words, NRS score increased with increasing age and NRS scores decreased with increasing BMI, calorie need and albumin levels. However, the numerical value of the score was not statistically significant in the malnutrition group (NRS score 3 and above). In addition, there was no statistically significant relationship between NRS score and prealbumin, CRP and length of hospital stay.

Study Limitations

The study was done for a certain hospital and cannot be generalized to the whole universe. Patient profiles, hospital conditions and procedures may vary. All of the biochemical parameters of the patients were not assessed and the biochemical parameters were evaluated with the available data. The length of hospital stay was evaluated not as the total length of hospital stay of the patient due to the primary diagnosis but as the period starting from the evaluation of the NSU.

CONCLUSION

Our study emphasized the importance of absolute review of BMI, albumin and CRP levels in order to evaluate the malnutrition of patients with detected malnutrition by NRS-2002. In addition, in patients with malnutrition according to NRS-2002 score, this score does not change the biochemical values, BMI and length of hospital stay when it is between 3-7 points. We think that it is important to monitor the patients closely by establishing NSUs in hospitals, especially in the neurology and oncology clinics, since the detection of malnutrition and nutritional support affect the clinical course.

Table 4. Mean and standard deviation of continuous variables with and without malnutrition

	NRS score				P
	No malnutrition		Malnutrition		
	Mean	SD	Mean	SD	
Age (year) **	58.92	12.75	72.46	14.97	0.001
Albumin (g/dL)***	3.18	0.64	2.87	2.30	0.006
Prealbumin (g/dL)**	15.80	4.66	11.75	5.91	0.131
CRP (mg/L)***	60.48	69.58	88.36	73.55	0.050
BMI**	25.31	5.61	22.65	4.47	0.005
Length of hospital stay***	9.04	8.22	12.85	13.88	0.242

:Independent samples, *: Mann-Whitney U, SD: Standard deviation, BMI: Body mass index, NRS: Nutrition risk screening, CRP: C-reactive protein

Table 5. The correlation analysis between NRS score and the variables

		NRS	Age	Albumin	Prealbumin	CRP	BMI	Length of hospitalization	Calorie	
Spearman's rho	NRS	r	1.000	0.301	-0.196	-0.082	0.006	-0.200	-0.054	-0.163
		p	0.000	0.000	0.000	0.290	0.908	0.000	0.255	0.001
		n	450	450	364	169	368	450	450	450

NRS: Nutrition risk screening, CRP: C-reactive protein, BMI: Body mass index

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Izmir Bozyaka Training and Research Hospital, University of Health Sciences (no: 3, dated: 09.08.2016).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.Ü., Concept: Y.E.K., C.İ., Design: O.Ü., Y.B., Data Collection or Processing: Y.E.K., Y.B., C.İ., Analysis or Interpretation: O.Ü., Y.E.K., P.O., Literature Search: O.Ü., P.O., Writing: O.Ü., P.O.

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Is there any Relationship Between Acquired Premature Ejaculation and Blood Vitamin B12 or Folic Acid Levels?

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Abstract

Objective: To investigate the relationship between acquired premature ejaculation (PE) and serum vitamin B12 or folic acid levels.

Methods: A total of 93 patients with acquired PE and 69 controls without PE were included the study. All patients fulfilling the criteria of the International Society for Sexual Medicine Committee were considered to have acquired PE. Serum vitamin B12 and folic acid levels were evaluated in all men included in the study.

Results: Compared to controls, vitamin B12 levels were lower in patients with acquired PE (336.5±142.9 pg/mL vs. 356.0±162.5 pg/mL); however, there was no statistically significant difference between the two groups (p=0.576). There was no significant difference in folic acid levels between patients with acquired PE and controls (7.5±3.4 ng/mL vs. 7.3±3.1 ng/mL, p=0.853).

Conclusion: There is no relationship between serum vitamin B12 and folic acid levels and acquired PE. The evaluation of these vitamins should not be recommended to explore the etiology and risk factors of acquired PE.

Keywords: Intravaginal ejaculation latency time, premature ejaculation, vitamin B12, folic acid

INTRODUCTION

Premature ejaculation (PE) is the most common sexual dysfunction in men (1). Although its prevalence varies according to different criteria, this rate is reported as 4-39% (2). In a cross-sectional study carried out in Turkey, the prevalence of PE was found to be 20% (3). However, despite these high prevalence rates, the definition and subtypes of PE are still ongoing. According to the definition made by the International Society for Sexual Medicine (ISSM) in 2014, lifelong PE was defined as “ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration from the first sexual experiences” and acquired PE was defined as “a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less”. According to this definition, “the inability to delay ejaculation on all or nearly all vaginal penetrations”

and “negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy” defined as PE (4). In addition to these definitions, Waldinger (5) classified two distinct subgroups as natural variable PE and subjective PE. Natural variable PE is defined as “PE not always occurring and not seen in every sexual intercourse” and subjective variable is defined as “subjective perception of PE while actually having a normal or even extended ejaculation time”. However, these two subgroups are not considered within the PE definition. Basile Fasolo et al., (6) reported that acquired PE was more common (14.8% vs. 4.5%) than lifelong PE, whereas Serefoglu et al., (7) reported that lifelong PE was more common (62.5% vs. 16.1%).

Although the underlying causes of lifelong PE are usually acquired neurobiological dysfunctions, correctable medical pathologies



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are often included in the etiology of acquired PE. Some of these pathologies are anxiety (8), psychological or relational problems (8), erectile dysfunction (ED) (9), chronic prostatitis (10), hyperthyroidism (11) and various drugs (12). For these reasons, the treatment response in acquired PE to is better than lifelong PE (13, 14). It has been reported by many authors that anxiety is an important risk factor for acquired PE (15, 16). It has been shown that anxiety activates the sympathetic nervous system, thereby reducing the ejaculatory threshold as the ejaculation emission phase occurs earlier (15). It is also known that nitric oxide and serotonergic neurotransmitters play a role in the ejaculatory cascade and that pathological condition or drugs affecting this cascade may affect the duration of ejaculation (15).

Vitamin B12 and folic acid are essential vitamins, which are necessary for various metabolic functions in the central nervous system and have regulatory roles on mood. In the deficiency of vitamin B12 and folic acid, methylation of neurotransmitters such as serotonin and dopamine is impaired and hyperhomocysteinemia occurs. As a result of these two conditions, mental disorders such as anxiety and depression may develop (17). It is also known that vitamin B12 plays a complementary role in the metabolism of serotonin and nitric oxide (18, 19). In addition, folic acid deficiency was associated with decreased 5-hydroxytryptamine (5-HT) activity and weak response to selective serotonin reuptake inhibitors (SSRIs) has been shown (20).

This study was planned to compare the levels of vitamin B12 and folic acid in patients with acquired PE and healthy controls.

METHODS

This single-center, prospective, observational study was performed in accordance with the and Helsinki Declaration and informed consent of the patient. This study by approved to the decision of the Ethics Committee of Clinical Researches of İstanbul Okmeydanı Training and Research Hospital of the University of Health Sciences (approval no: 963). One hundred and sixty-two patients who applied to the andrology outpatient clinic between January 2017 and June 2017 were analyzed. The study included 93 patients with acquired PE and 69 controls without any PE symptoms. Inclusion criteria were as follows: between the ages of 20 and 60, having a permanent and heterosexual relationship within the last 6 months, and having acquired PE according to the 2014 ISSM criteria (4). Patients with a) lifelong PE, b) chronic disease or psychiatric and neurological disorder that may affect sexual function, c) history of pelvic/perineal trauma or surgery, d) active urinary tract infection or chronic prostatitis, e) SSRI, alpha

blocker, phosphodiesterase type 5 inhibitor and anticholinergic drug use and f) supplementary vitamin B12 or folic acid use were excluded from the study.

All participants were questioned with a Turkish version of the PE Diagnostic Tool (PEDT) form (21). In all participants, partner-assisted intravaginal ejaculation latency time (IELT) was recorded with a stopwatch. The validated Turkish version of International Index of Erectile Function-5 (IIEF-5) was used to evaluate the erectile function (22, 23). Patients with severe and moderate ED according to the IIEF-5 score were not included in the study. Body mass index (BMI), partner age, frequency of sexual intercourse, smoking and alcohol consumption and various comorbidities were recorded.

For the evaluation of vitamin B12 and folic acid levels, blood samples were obtained between 8:00 and 10:00 am after 8-10 hours of night fasting.

All statistical analyzes were performed using SPSS 22 (IBM Co., Armonk, NY, USA). Mean, standard deviation, median, minimum, maximum and frequency values were used for descriptive statistics of the data. The distribution of variables was analyzed by Kolmogorov-Smirnov test. Independent Samples t-test and Mann-Whitney U test were used for quantitative analysis of independent data and chi-square test was used for the analysis of qualitative independent data.

RESULTS

Of the 162 men included in the study, 93 had acquired PE. The remaining 69 men constituted the control group. Demographic and clinical characteristics of the study population are given in Table 1. There was no difference between the mean age of the patients with acquired PE and controls (40.0 ± 7.2 vs. 40.6 ± 4.8 , $p=0.876$). Similarly, no difference was observed between the two groups in terms of partner age, BMI and frequency of monthly sexual intercourse. There was no difference between two groups in terms of smoking, alcohol consumption and various comorbidities (diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia). The IIEF-5 score was not different between the two groups (22.5 ± 6.4 vs. 22 ± 4.2 , $p=0.912$).

The mean PEDT score was 15.3 ± 3.6 in the PE group and 9.9 ± 4.7 in the control group ($p < 0.001$). As expected, mean IELT was significantly lower in the acquired PE group compared to the control group (32.3 ± 22.4 sec. vs. 221.7 ± 166.5 sec., $p < 0.001$) (Table 2).

Mean folic acid levels were 7.5 ± 3.4 ng/mL in the PE group and 7.3 ± 3.1 ng/mL in the control group. This difference was

not statistically significant ($p=0.853$). Vitamin B12 levels were lower in the acquired PE group, but no statistically significant difference was observed between the two groups (336.5 ± 142.9 pg/mL vs. 356.0 ± 162.5 pg/mL, $p=0.576$) (Table 2).

DISCUSSION

Studies on somatic and neurobiological factors to explain the etiology of PE have increased in the last two decades. While unexplained neurobiological dysfunctions are suggested in the etiology of life-long PE, the etiology of acquired PE often includes causes with better response to medical therapy (14). In our study, we planned to study only patients with acquired PE to demonstrate the association between PE and vitamin B12 and folic acid levels.

Folic acid and vitamin B12 have important roles in 5-HT, dopamine and noradrenaline metabolism (19, 24). It is known that serotonergic, dopaminergic and adrenergic neurons play a role in the complex mechanism of ejaculation control (25).

Folic acid supplementation has been shown to increase the level of 5-hydroxyindolacetic acid, the main metabolite of 5-HT in cerebrospinal fluid (26). It is thought that these vitamins may be effective in the treatment of PE, especially if the relationship between folic acid or vitamin B12 can be demonstrated. However, in our study, no statistically significant difference was observed between two groups, although vitamin B12 level was lower in patients with acquired PE. Another study from Turkey has shown a significant relationship between vitamin B12 and PE (27). However, in this study, patients with acquired PE or lifelong PE were not mentioned separately and this study was conducted with lower number of patients.

It has been shown in several studies that anxiety and depression and PE have a bidirectional relationship (28-31). In particular, it is stated that anxiety reduces the time of ejaculation by affecting the emission phase by activation of sympathetic nervous system. In our study, there was no significant difference in the evaluation

Table 1. Demographic and clinical characteristics of the study population

	Acquired PE group (n=93)		Control group (n=69)		p
	Mean \pm SD median (range)		Mean \pm SD median (range)		
	n - %		n - %		
Age (year)	40.0 \pm 7.2	41 (21-59)	40.6 \pm 4.8	40 (23-60)	0.876
Partner age (year)	35.3 \pm 7.2	35 (21-44)	34.0 \pm 4.2	36 (26-48)	0.156
BMI (kg/m ²)	27.5 \pm 4.4	27 (17.5-43)	27.9 \pm 3.4	26.4 (18-37.6)	0.531
Sexual intercourse frequency (month)	6.3 \pm 3.1	6 (3-16)	7.2 \pm 4.1	6 (2-17)	0.323
Smoking	41-44.08%		35-50.7%		0.331
Alcohol consumption	10-10.7%		9-13.04%		0.234
IIEF-5 score	22.5 \pm 6.4	22 (15-23)	22 \pm 4.2	20 (14-25)	0.912
Comorbidities					
DM	7-7.5%		4-5.7%		0.715
Hypertension	7-7.5%		6-8.6%		0.753
CVD	2-2.1%		2-2.8%		0.876
Dyslipidemia	4-4.3%		4-5.7%		0.445

PE: Premature ejaculation, SD: Standard deviation, BMI: Body mass index, IIEF-5: International Index of Erectile Function-5, DM: Diabetes mellitus, CVD: Cardiovascular disease

Table 2. Evaluation of premature ejaculation and folic acid and vitamin B12 levels

	Acquired PE group (n=93)		Control group (n=69)		p
	Mean \pm SD median (range)		Mean \pm SD median (range)		
	n - %		n - %		
IELT (second)	32.3 \pm 22.4	25.6 (0-124)	221.7 \pm 166.5	221.7 (82-876)	<0.001
PEDT score	15.3 \pm 3.6	15 (7-23)	9.9 \pm 4.7	10 (3-14)	<0.001
Vitamin B12 (pg/mL)	336.5 \pm 142.9	316.6	356.0 \pm 162.5	289.9	0.576
Folic acid (ng/mL)	7.5 \pm 3.4	6.9	7.3 \pm 3.1	6.9	0.853

PE: Premature ejaculation, SD: Standard deviation, IELT: Intravaginal ejaculatory latency time, PEDT: Premature ejaculation Diagnostic Tool, IIEF-5: International Index of Erectile Function-5

of depression in both groups. In a study conducted with hospital anxiety and depression scale, a significant relationship was found between PE and anxiety (32). In our study, a direct interpretation about the relationship between folic acid and vitamin B12 and anxiety-PE relationship cannot be made between patients with acquired PE and controls, as anxiety was not questioned in our study.

Nitric oxide has an important role in the relationship between sympathetic nervous system and ejaculation (15). In addition to 5-HT metabolism, folic acid and vitamin B12 are known to be complementary factors in nitric oxide metabolism (33, 34). As a result of the studies to be carried out in the future, it may be possible to prolong the time of ejaculation with folic acid and vitamin B12 supplements.

One of the risk factors for acquired PE is ED. In a prevalence study conducted with 12,333 men from three countries, the rate of ED in men with PE was 31.9% and this rate was reported to be 11.8% in men without PE (35). In our study, no significant difference was observed between IIEF-5 scores and PE. Jannini et al., (36) stated that ED and PE could be the cause of each other (36). The reason for no correlation between IIEF-5 scores and PE in our study might be due to patients with moderate and severe ED were not included in our study and only patients with acquired PE complaints were included.

In the evaluation of PE, IELT alone may not be sufficient for diagnosis. Therefore, various questionnaires were developed. PEDT was used in our study and this questionnaire has the largest database (21). In addition, IELT was measured with a stopwatch and the mean time was 221.7 seconds (3.7 min) in healthy males. In two multicenter studies, including Turkey, the median IELT in the general population was measured as 5.4 min and 6.0 min, respectively (37, 38).

In our study, no significant difference was observed between two groups in terms of demographic characteristics. Age, partner age, frequency of sexual intercourse, smoking and alcohol consumption were similar in both groups. Gao et al., (14) showed a relationship between acquired PE and high BMI. However, there was no significant relationship between BMI and PE in our study.

Study Limitations

There are several limitations in our study. First, healthy men in the control group may not represent the general population. Second, the number of patients in both groups is relatively low. Our results need to be confirmed by large-scale studies. In addition, the lack of the evaluation of the anxiety and partner's

sexual dysfunction, which are among the etiologies of PE, is one of the main limitations of the study.

CONCLUSION

In our study investigating the relationship between acquired PE and vitamins B12 and folic acid, it was shown that both vitamins were not associated with PE. However, large-scale clinical and observational studies are needed to demonstrate this relationship indirectly through psychoneuroendocrine routes.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences İstanbul Okmeydanı Training and Research Hospital Ethics Committee (approval number: 963).

Informed Consent: Informed consent from was patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.L.C., R.B.D., O.C., Concept: H.L.C., Design: H.L.C., Data Collection or Processing: H.L.C., R.B.D., O.C., H.A.A., İ.A., M.G.C., S.Ö., Analysis or Interpretation: H.A.A., İ.A., M.G.C., S.Ö., Literature Search: H.L.C., R.B.D., Writing: H.L.C.

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

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Results of the Bethesda System in Patients Undergoing Thyroidectomy-A Single-Center Experience

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Abstract

Objective: To compare preoperative fine needle aspiration biopsy (FNAB) and postoperative histopathological findings in patients undergoing thyroidectomy and to validate the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Methods: Data from 366 patients who underwent thyroidectomy between 2014-2016 were analyzed retrospectively and the variables related to thyroid cancer were investigated.

Results: Of 366 patients, 44 (12%) were male and 322 (88%) were female. Regarding FNAB results according to TBSRTC, 23 (6.3%) patients had category I, 79 (21.6%) had category II, 128 (35%) had category III, 113 (30.9%) had category IV, nine (3.8%) patients had category V and 14 (2.5%) had category VI cytology. Histopathological examination revealed thyroid cancer in 65 (17.7%) patients. The Bethesda System was found to have a sensitivity of 73.9% and a specificity of 96%. There was no association between thyroid cancer and other variables except male gender.

Conclusion: Although TBSRTC has an acceptable sensitivity and specificity, the risk of malignancy in category III and IV patients may vary. Therefore, multidisciplinary approach should be considered during treatment planning and surgical treatment option should be kept in mind.

Keywords: Fine needle aspiration biopsy, Bethesda System, thyroid nodule, thyroid cancer, thyroidectomy

INTRODUCTION

The incidence of thyroid nodules increased to 50%-70% with the use of high-resolution ultrasonography (US) (1). The incidence of cancer in thyroid nodules varies between 2% and 15% (2). Fine needle aspiration biopsy (FNAB) has an important role in the evaluation of thyroid nodules and the detection of cancer risk. Early diagnosis of clinically insignificant thyroid cancers is possible with FNAB, and patients are protected from unnecessary surgery and associated complications (3). With the widespread use of FNAB, conflicting reports between pathologists have started to emerge in the evaluation of cytology. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was developed in 2007 to eliminate terminological confusion. According to TBSRTC, FNAB results are divided into six categories: non-diagnostic, benign, atypia of undetermined significance/

follicular lesion of undetermined significance, follicular nodule/suspicious follicular nodule, suspicious for malignancy and malignant (Table 1) (4).

Central and Eastern Black Sea region are endemic regions for thyroid nodules. The aim of this retrospective analysis was to validate TBSRTC by comparing FNAB and histopathological (HP) results of 366 patients who underwent total thyroidectomy in Samsun Training and Research Hospital General Surgery Clinic between 2014-2016.

METHODS

The demographic characteristics of the patients, FNAB results according to TBSRTC, characteristics of single nodule or multinodular goiter, nodule diameters and HP results were recorded. All biopsies were taken under the guidance of an



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US by a radiologist with a 22 gauge needle and 10 cc injector in outpatient clinic settings. TBS was used for cytological classification. Repeat FNAB was planned for patients who had a non-diagnostic FNAB cytology. Follow-up or surgical treatment was suggested to patients with a second non-diagnostic FNAB cytology. Patients with nodule growth or suspicious US findings (solid hypochoic nodules or cystic, microcalcified nodule with extra-thyroidal extension and irregular margins) during the follow-up period and patients who accepted surgery instead of follow-up were included in the study. Thyroidectomy was performed due to various indications other than cancer (cosmetic causes, trachea compression, hyperthyroidism) in patients with benign cytology. The HP findings of the patients were compared with the preoperative cytology results. Incidence of malignancy, suspected malignancy with benign cytology in TBSRTC, sensitivity and specificity of malignant cytology category, and the positive predictive and negative predictive values (PPD and NPD) were calculated in groups divided according to TBSRTC. In addition, the presence of a significant relationship between cancer incidence and age, gender, single nodule/multinodularity and nodule diameter parameters was investigated.

Statistical Analysis

SPSS 23.0 (IBM Corporation, Armonk, New York, United States) program was used for statistical analysis. While mean, standard error and minimum-maximum values were used for quantitative variables, categorical variables were expressed as n (%). Independent samples-t test was used for comparing the quantitative data of the two groups and chi-square test was used to compare the categorical data. P<0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 50.47 (18-79) years. Forty-four (12%) patients were male (88%) and 322 were female. The median nodule diameter was calculated as 21.44 mm (4-65). A single nodule was detected in US in 152 (41.5%) patients, while

the remaining 214 (58.5%) patients had multinodular goiter (Table 2). According to TBSRTC, 23 (6.3%) patients had category I, 79 (21.6%) had category II, 128 (35%) had category III, 113 (30.9%) had category IV, nine (3.8%) patients had category V and 14 (2.5%) had category VI cytology (Figure 1). HP examination revealed thyroid cancer in 65 (17.7%) patients. Papillary microcarcinoma was detected in 30 of 65 patients (8.2%) and papillary carcinoma in 34 patients (9.3%). Medullary thyroid cancer was seen in one (0.3%) patient. Of the remaining 301 patients, 290 (79.2%) had benign nodules, six (1.6%) had follicular adenoma and five (1.4%) had Hurthle cell adenoma. Table 3 shows the HP results of the patients divided into six categories according to TBSRTC after thyroidectomy. Thyroid cancer was found in six of 79 patients with benign cytology. Considering category II, V and VI, TBSRTC was found to have a sensitivity of 73.9% and a specificity of 96%. In addition, PPD was calculated as 73.9%, NPD was 92.4% and accuracy was 88.2%. The incidence of cancer was found to be higher in men compared to women (31.8% vs. 18.8%, p=0.009).

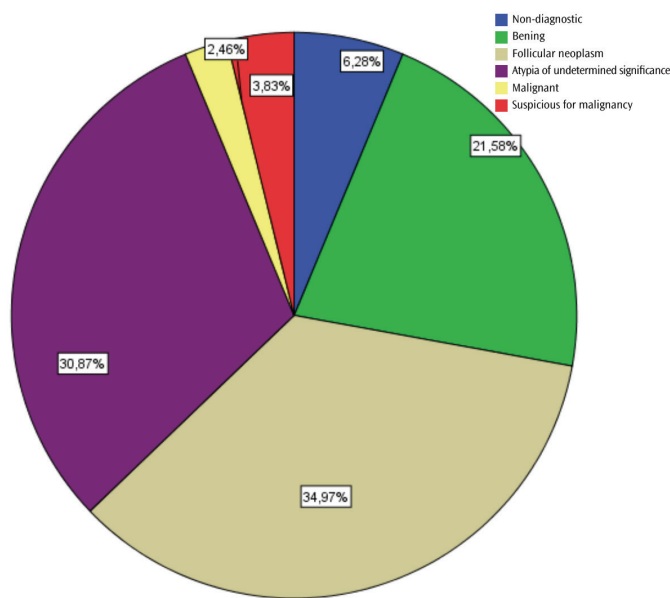


Figure 1. Distribution of FNAB results according to Bethesda criteria
FNAB: Fine needle aspiration biopsy

Diagnostic category	Risk of malignancy (%)	Treatment recommendation
Non-diagnostic or unsatisfactory	1-4	Repeat fine needle aspiration biopsy
Benign	0-3	Follow-up
Atypia of undetermined significance/follicular lesion of undetermined significance	~5-15	Repeat fine needle aspiration biopsy
Follicular neoplasm	15-30	Lobectomy
Suspicious for malignancy	60-75	Lobectomy/near-total thyroidectomy
Malignant	97-99	Near-total thyroidectomy

There was no statistically significant difference between benign and malign HP groups in terms of nodule diameter, single nodule or multinodular goitre on US findings and age ($p=0.097$,

$p=0.267$, $p=0.863$, respectively) (Table 4). According to FNAB results, when the patients in category III and IV were evaluated separately, male gender was found to be a risk factor for thyroid cancer in the category III group ($p=0.015$); no relationship was found between thyroid cancer and age, gender, nodule diameter and nodular/multinodular goiter in the category IV (Table 5).

Table 2. Distribution of patients according to age, gender, nodule diameter and ultrasonography results

Age: mean (min-max, SD)	50.47 (18-79, 13.073)
Gender	
Male (%)	44 (12%)
Female (%)	322 (88%)
Nodule diameter (mm): Mean (min-max, SD)	21.44 (4-65, 10.864)
Ultrasonography	
One nodule (%)	152 (41.5%)
Multinodular (%)	214 (58.5%)

DISCUSSION

In the last half century, as in all over the world, the incidence of thyroid cancer increases and mortality due to thyroid cancer decreases. The most important reason for the increase in the incidence of thyroid cancer is the development of diagnostic methods (5). Nowadays, the FNAB is widely used as the first-line diagnostic method in the management of thyroid

Table 3. Histopathological results of the patients categorized by the Bethesda System

Bethesda category	Histopathological results						Total	Risk of malignancy (%)
	B	FA	HCA	PMC	PC	MTC		
I	16	3	2	0	2	0	23	8
II	72	0	1	3	2	1	79	7.6
III	99	1	2	13	13	0	128	20.3
IV	97	2	0	9	5	0	113	12.3
V	3	0	0	2	4	0	9	66.6
VI	3	0	0	3	8	0	14	78.5

B: Benign, FA: Follicular adenoma, HCA: Hürthle cell adenoma, PMC: Papillary microcarcinoma, PC: Papillary carcinoma, MTC: Medullary thyroid carcinoma

Table 4. Comparison of patients divided according to histopathological results

	Benign	Malign	p
Age (mean, SD)	50.52 (13.025)	50.22 (13.389)	0.916
Gender			0.009
Male: n (%)	30 (68.2)	14 (31.8)	
Female: n (%)	271 (83.7)	51 (16.3)	
Nodule diameter: mm (mean, SD)	21.88 (10.858)	19.42 (10.743)	0.680
NG/MNG (%)	121/180 (33/49)	31/34 (8.4/9.2)	0.266

NG: Nodular goiter, MNG: Multinodular goiter, SD: Standard deviation

Table 5. Comparison of AUS and FN subgroups

	AUS			FN		
	Benign	Malign	p	Benign	Malign	p
Age (mean, SD)	49.24 (12.596)	53.69 (15.278)	0.082	49.79 (13.485)	46.79 (10.349)	0.230
Gender			0.015			0.77
Male: n (%)	7 (54.9)	6 (46.1)		7 (70)	3 (30)	
Female: n (%)	95 (82.7)	20 (17.3)		92 (89.4)	11 (10.6)	
Nodule diameter: mm (mean, SD)	21.21 (11.764)	20.77 (11.368)	0.442	20.30 (9.261)	17.29 (6.787)	0.129
NG/MNG (%)	43/59 (33.5/46)	12/14 (9.3/10.9)	0.713	39/60 (34.5/53)	8/6 (7/5.3)	0.207

AUS: Atypia of undetermined significance, FN: Follicular neoplasm, NG: Nodular goiter, MNG: Multinodular goiter, SD: Standard deviation

nodules according to US findings. The incidence of cancer after thyroidectomy has increased from 10-20% to 50%. Thanks to the FNAB, unnecessary surgeries and associated complications and cost decreased significantly (6). The widespread use of FNAB has brought along the need for standardization in the reporting of cytology results, for this purpose, TBSRTC was developed in 2007 and the cytology results were divided into six categories.

In order to accept the FNAB material sufficient for diagnosis, the material should consist of minimum 5-6 separate groups consisting of at least 10 follicular epithelial cells (4). In studies conducted, 89-95% of FNAB samples from thyroid nodules were reported to be sufficient for diagnosis. While 55-74% of the cytology examinations are reported as category I, category IV and V vary between 2-5% (7-10). Similar data were obtained in our study. In our series, 93.7% of the samples were sufficient for diagnosis and the rate of category IV-V was 6.2%. However, unlike other studies, category II rate was 21.5% in our study. The reason for this difference is the exclusion of category II patients who were not indicated for surgical treatment and inclusion of patients who underwent thyroidectomy only. The prevalence of cancer in category II cytology varies between 1-3.2% in large case series and meta-analyzes (11-16). In our study, preoperative cytology of 79 patients was reported as category II and six patients (6.32%) had thyroid cancer. In this group, cancer was detected in only one of 32 patients with single nodule and in five of 47 patients with multiple nodules. The cytological examination of the patients with multinodular goiter is taken from the dominant nodule and cancer is observed in non-dominant nodules in these patients. It is natural that the incompatibility with the literature is due to this reason. Regarding 32 patients with single nodules, the incidence of cancer is 3.1%, which is parallel to the literature.

The incidence of cancer in category 5 and category 6 cytology varies between 60-75% and 97-99%, respectively, in the original article in which TBSRTC was defined and in subsequent meta-analysis with a considerable number of cases (4, 8, 17). In our study, these rates were determined as 66.6% and 78.5%, respectively. In our cases, the incidence of cancer, especially in category VI cytology, is low compared to the literature. There may be two reasons for this difference: the experience of the pathologist in TBSRTC and the low number of cases. However, considering the accuracy of 88.6% when the categories II, V and VI are considered together, we believe that TBSRTC can be used safely in these categories. In the light of the information obtained from the guidelines, the general approach in category II cases is follow-up and surgical treatment in the presence

of indications for surgery other than cancer. In contrast, the approach is surgical treatment in category V and VI. The main problem in clinical practice is category III and IV cases.

The definition "atypia of undetermined significance/follicular lesion of undetermined significance" is used for cytology specimens consisting of cells with unexpected structural and nuclear atypia in benign changes and with no risk other than that (18). This cytological description constitutes 1-27% of FNAB results (19). The cancer risk in Bethesda category III is reported to be between 5% and 15%, although many studies have reported that cancer rates vary between 17-39% (4, 20-27). In our study, the incidence of thyroid cancer was 20.3% in patients with category III cytology. In the American Thyroid Association guideline, considering the suspected clinical and sonographic characteristics, category III patients are advised to undergo repeat biopsy or molecular study instead of follow-up or diagnostic surgery (28).

In some studies, it has been suggested that core biopsy is more useful and tolerable than FNAB (29, 30). However, the American Association of Clinical Endocrinologists, the Italian Association of Clinical Endocrinologists and European Thyroid Association joint guideline concludes that core biopsy does not provide additional benefit but increases morbidity. Again in this guide, it is emphasized that malignancy criteria (head and neck radiation history, family history, <14->70 years, male gender, fixed nodule, fast growing nodule, etc.) have low predictive value and that there is yet not enough data to suggest that US elastography can be used routinely. In addition, it was emphasized that surgery should be considered primarily in these cases, considering that molecular tests are expensive and can be performed in only private centers (31). It has also been shown that some of the patients that underwent repeat FNAB and interpreted as benign had malignancy after resection (32). In these patients, it would be most appropriate to plan the treatment by a multidisciplinary council with a surgeon, medical endocrinologist, radiologist and cytopathologist with considering the opinion of the patients. Another category "follicular nodule/suspicious follicular nodule" constitute approximately 10-25% of all FNABs. In various studies, malignancy rates in category IV cases have been reported between 18-28% (9, 33-35). In our study, the rate of malignancy was lower than expected (12.3%).

In general, there are some differences between TBSRTC and our results. Among the reasons for these differences, the experience of the cytopathologist, FNAB method and the endemic nature of our region can be considered. When risk factor analysis

was performed, only male gender was found to be significant and other parameters were statistically insignificant. For the validation of TBSRTC, cohort studies with larger cases are needed in our region.

CONCLUSION

Thyroid FNAB has an important role in the management of thyroid nodules. Although TBSRTC is guiding, it may be incompatible with published studies. This difference is directly related to the experience of the pathologist, the method of FNAB and even the resources of the healthcare center. In conclusion, the clinician should act with other departments in the management of a thyroid nodule and should be in a patient-oriented multidisciplinary approach.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: External and internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., Ö.B., K.Y., Concept: S.O., Ö.B., Design: S.O., K.Y., Data Collection or Processing: S.O., Ö.B., K.Y., Analysis or Interpretation: S.O., K.Y., Literature Search: S.O., Ö.B., K.Y., Writing: S.O., Ö.B.

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Surgical Treatment Results in Craniofacial Dermoid Cysts: Retrospective Analysis of 29 Cases

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Abstract

Objective: Dermoid cysts are developmental malformations originating from ectoderm and mesoderm. They are congenital and usually localized in the head and neck region. Their walls are covered with squamous epithelium and may contain different skin patches and tissues (multiple sebaceous glands, hair follicles, sweat glands, fat, nail, eye, teeth, cartilage). The purpose of this study was to present an approach to the masses in the head and neck region, to evaluate the relationship between preoperative imaging, final pathology and differential diagnosis, and to discuss how treatment planning should be done.

Methods: In this study, 37 patients, who admitted to our clinic for masses in the head and neck region and who underwent surgery after necessary consultations and preoperative evaluation between January 2010 and July 2017 were retrospectively reviewed. Patients were evaluated in terms of age, gender, lesion size, lesion location, preoperative imaging, intracranial involvement, treatment and complications.

Results: Of the 29 patients included in this study, 15 were male (51.7%) and 14 were female (48.2%). The age of the patients ranged from 1 to 28 years and the mean age was 10 years. Twenty-two of the lesions were localized on the lateral side of the eyebrows (75.8%), two on the glabella (6.8%), two in the temporal region (6.8%), one in the occipital region (3.4%), one on the forehead (3.4%), and one in the medial canthal region (3.4%). At the time of admission, all patients complained of swelling under the skin at the localization of the lesion. At least one imaging modality, primarily computed tomography, was requested to assess intracranial involvement in all patients' preoperatively. The main reason for the removal of lesions was cosmetic problems.

Conclusion: Dermoid cysts are operated not only for the removal of poor cosmetic appearance, but also for the prevention of possible leakage and infection, for definite pathologic diagnosis and for prevention of secondary bone changes.

Keywords: Dermoid cyst, head and neck, intracranial involvement

INTRODUCTION

Dermoid cysts are congenital malformations originated from ectoderm and mesoderm. They are usually localized on the head and neck region, and trunk. They are lined by squamous epithelium and involve different types of skin-related structures such as multiple sebaceous glands, hair follicles, sweat glands, fat, nail, teeth, cartilage or bone structure. Dermoid cysts are often benign as they contain mature tissue. Squamous cell carcinoma in adults and endodermal sinus tumor in infants and children

are some rare malignant forms of dermoid cysts. Head and neck dermoid cysts constitute less than 10% of all dermoid cysts. There is no definite information on prevalence, racial selectivity and gender discrimination. However, most cases of dermoid cysts in the literature belong to the white race. In infants, they are usually found as subcutaneous masses throughout the embryonic skin fusion lines. The regions where they are commonly seen include periorbital (zygomaticofrontal suture), nasal (frontonasal suture and rhinion), intraoral (floor of the mouth), scalp (anterior fontanel and cranial sutures) and postauricular areas (1, 2).



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In this study, we aimed to retrospectively review our experience in terms of location, clinical findings and surgical treatments of dermoid cysts located in the head and neck region, to better define the characteristics of each subgroup and to establish a comprehensive treatment algorithm.

METHODS

In this study, a total of 37 patients, who were admitted to our clinic with a mass in the head and neck region, and who were operated after required consultations and preoperative evaluations between January 2010 and July 2017, were retrospectively reviewed. Patients were evaluated in terms of age, gender, size and location of lesion, preoperative imaging results, intracranial involvement, treatment and complications. Preoperative radiology reports were examined, postoperative pathology reports were obtained from the archives and patients with a definite pathology report of dermoid cyst were identified. Eight patients (22.8%) were excluded from the study due to mismatch of the initial diagnosis and definite pathology results. In order to prevent potential complications or relapse, patients were invited for control every 3 months for at least 1 year. At the end of this period, no recurrence, pathological scar and additional complications were observed. The details, characteristics on admission and management of the patients are given in Table 1. In the direct excisional approach, the incision was made on the periorbital masses on the lateral edge of the eyebrows and in the hairline for the masses on the scalp. In unsuitable cases, an incision was made in the middle of the masses to create minimal stress. If the mass was close to a nerve, that nerve was dissected and preserved. After dissection, the mass was excised and checked for any bone or orbital extension. All excised masses were sent for pathological examination.

RESULTS

Of the 29 patients included in this study, 15 were male (51.7%) and 14 were female (48.2%). The ages of the patients ranged from 1 to 28 years and the mean age was 10 years. Twenty-two of the lesions were localized lateral to eyebrow (75.8%), two were on glabella (6.8%), two were in the temporal region (6.8%), one was in the occipital region (3.4%), one was on the forehead (3.4%), and one was in the medial canthal region (3.4%). The mean lesion size was 13.2x7.03 mm (between 18 and 4 mm). Regarding localization of the lesions, 14 (48.2%) were on the right side, 11 (37.9%) were on the left side and 4 (13.7%) were midline. On admission, there was swelling under the skin at the lesion localization. No pain or discharge was reported over the

lesion. In the preoperative evaluations, all patients had at least undergone one imaging modality: computed tomography (CT), ultrasonography (USG) or magnetic resonance imaging (MRI). Two patients (6.8%) had both CT scan and MRI. Nine patients (31.03%) had only USG, 12 patients (41.3%) had USG and CT scan, four patients (13.7%) had USG and MRI, and two patients (6.8%) had USG, MRI and CT scan. Also, the comparison between initial diagnoses based on preoperative imaging and postoperative pathology results are shown in Table 2.

The main reason for the removal of the lesions was cosmetic problems. All patients were operated under general anesthesia. The lesions were excised by proper incision through the skin and the defects were closed primarily. Pathological examination of all lesions was performed. No complications were observed. All the masses were superficial and none had intradural or intracranial extension. In one patient, the mass was compressing the temporal muscle, but there was no muscle perforation or deeper penetration. In one case, the cyst was fistulated into the orbita from the lateral wall of the orbital cavity (Figures 1, 2). In one patient, the mass caused erosion of the occipital bone, and bone was trimmed and bone wax applied. No cutaneous fistula or signs of inflammation were observed. Dermoid cysts were reported in 29 (82.8%) of the 37 patients operated. In the remaining eight patients, definite pathology results were not dermoid cyst despite initial dermoid cyst diagnosis according to preoperative imaging reports. In six patients (16.2%), epidermoid cyst, in one patient (2.7%), juvenil hemangioma and in one patient (2.7%), pylomatrixoma were reported as definite pathology results.

DISCUSSION

Facial dermoids are generally sporadic but familial linkage has been described in the literature. There are two theories

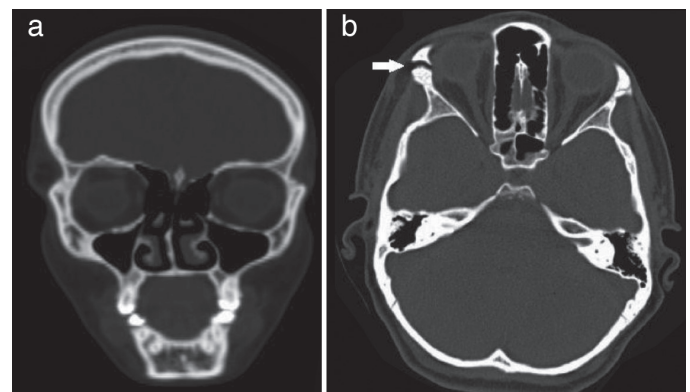


Figure 1. CT image of the dermoid cyst on the lateral right eyebrow in a 16-year-old patient. a) Coronal section, b) axial section; fistula into the orbita from the lateral wall of the right orbita (arrow)

Table 1. Demographic characteristics and clinical data summary of patients

Case	Age	Gender	Complaint	Intracranial involvement	Surgery	Preop scan	Lesion size	Complication
1	3	F	Mass on glabella	Absent	Excision-primary repair	USG	10x7 mm	Not observed
2	16	M	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, MRI	14x9 mm	Not observed
3	13	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, MRI	13x8 mm	Not observed
4	9	M	Mass on right postauricular region	Absent	Excision-primary repair	USG	15x7 mm	Not observed
5	10	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG	15x8 mm	Not observed
6	10	M	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG	13x7 mm	Not observed
7	10	F	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG	13x6 mm	Not observed
8	28	M	Mass on occipital region	Absent	Excision-bone wax-primary repair	USG, CT	17x9 mm	Not observed
9	14	M	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG, CT	14x6 mm	Not observed
10	17	F	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG, CT, MRI	15x7 mm	Not observed
11	4	M	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG	10x5 mm	Not observed
12	22	M	Mass on left postauricular region	Absent	Excision-primary repair	USG, CT, MRI	16x7 mm	Not observed
13	3	F	Mass on left medial canthal region	Absent	Excision-primary repair	USG	10x4 mm	Not observed
14	4	F	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG	11x5 mm	Not observed
15	9	M	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, CT	14x7 mm	Not observed
16	9	M	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG, CT	13x8 mm	Not observed
17	4	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, CT	12x6 mm	Not observed
18	15	F	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG, MRI	16x8 mm	Not observed
19	16	M	Mass on forehead	Absent	Excision-primary repair	USG, CT	17x8 mm	Not observed
20	3	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, CT	10x5 mm	Not observed
21	1	M	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, MRI	9x7 mm	Not observed
22	13	M	Mass lateral to right eyebrow	Absent	Excision-primary repair	CT, MRI	18x9 mm	Not observed
23	2	M	Mass on glabella	Absent	Excision-primary repair	USG, CT	11x8 mm	Not observed
24	16	M	Mass lateral to left eyebrow	Absent	Excision-primary repair	MRI, CT	15x8 mm	Not observed
25	3	M	Mass lateral to left eyebrow	Absent	Excision-primary repair	USG	12x6 mm	Not observed
26	1.5	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, CT	11x6 mm	Not observed
27	16	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, CT	15x9 mm	Not observed
28	16	F	Mass lateral to right eyebrow	Intraorbital involvement	Excision-primary repair	USG, CT	11x7 mm	Not observed
29	15	F	Mass lateral to right eyebrow	Absent	Excision-primary repair	USG, CT	11x7 mm	Not observed

F: Female, M: Male, USG: Ultrasonography MRI: Magnetic resonance imaging, CT: Computed tomography

about the embryological origin of craniofacial dermoids. The first is the superficial sequestration theory described by Bland-Sutton in 1893. The second and more widely accepted theory is the prenasal space theory described by Grunwald in 1910. This theory focuses on nasofrontal fontanelle formed by intramembranous ossification between frontal and nasal bones (2). Frontozygomatic dermoid cysts are superficial masses in zygomaticofrontal suture. They are usually removed by simple direct excision. Dermoid cysts contain histologically dermal adnexal structures such as intraluminal keratin and pilosebaceous units (3-5). Epidermal cysts are similar to dermoid

cysts, but do not contain pilosebaceous units in the cyst wall. Seven percent of dermoid cysts occur in the craniofacial region (5). Dermoids were topographically divided into three subgroups as frontotemporal region, occipital region and nasoglabellar region by Bartlett et al., (6) in 1993. Dermoid cysts in the frontotemporal region are the most common subgroup and are located in the lateral eyebrow region. If not infected, they emerge as slow-growing asymptomatic masses. Dermoid cysts in this region and the orbital region are typically superficial lesions, but nasoglabellar dermoid cysts, especially those under the nasofrontal suture line, often exhibit sinus tract and intracranial extension (7). In another study by Pryor et al., (8) they enrolled 49 pediatric patients and it was observed that dermoid cysts were mostly (61%) seen in the periorbital region. In our study, the lesions were located in the periorbital region in 75.8% of the cases and in the medial canthal region in 3.4% of the cases. In another study, dermoid cysts around the orbita were examined and dermoid cysts were found to be located 70% over the superotemporal-zygomaticotemporal suture, 20% over the superonasal maxillo frontal suture and 5% in the nasal soft tissue (9). Orbital dermoid cysts may exhibit ocular symptoms such as proptosis and limitation of eye movements. Dermoid cysts create a non-inflammatory mass effect, show a slow growth pattern and compress the surrounding tissues. Histologically, rupture is around 50% and low-grade inflammation is observed in surrounding tissues (9). Twenty percent of the dermoid cysts on the cranial midline show intracranial extension. Embryologically, they develop as a result of the continuation of the connection between the ectodermal and neuroectodermal structures during closure of the frontal and orbital segments at 8-9 weeks. Bone erosion can be seen in dermoid cysts especially in the periorbital region (10). In a study of 70 patients by Sathanathan et al., (11) bone erosion was found in 87% of the patients and full-thickness bone defect was detected in 34% of the patients.

In adult patients, preoperative imaging is more important because the cysts are larger and the probability of complications is higher. In our study, the size of the current mass was less than 2 cm in all cases and no intracranial involvement was observed.

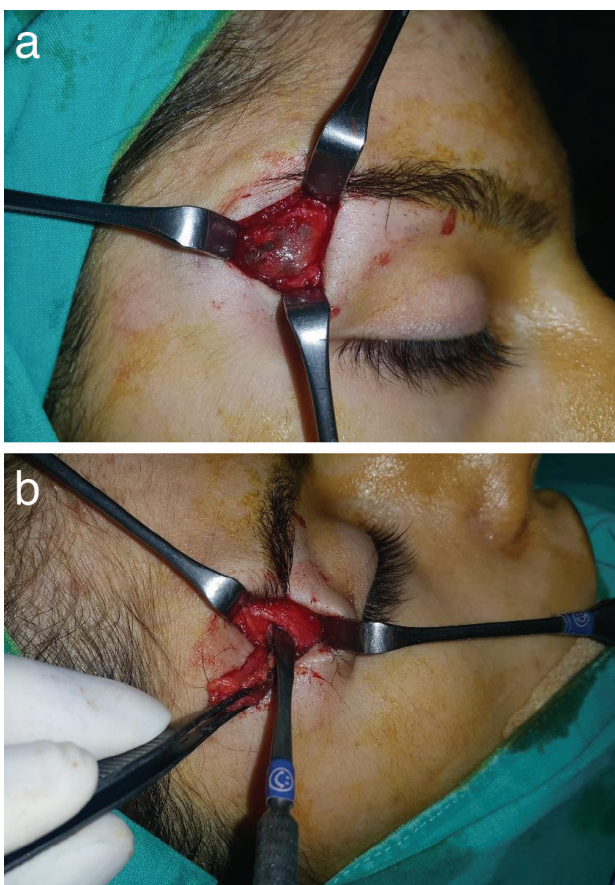


Figure 2. Peroperative photos of the patient in a) exploration of the dermoid cyst from the eyebrow incision, b) fistula into the orbita from the lateral wall during removal of the dermoid cyst

Number of case	Percent	Initial diagnosis on preoperative imaging (USG and MRI)	Postoperative pathology result
1	2.7%	Epidermal cyst? Dermoid cyst?	Juvenile hemangioma
1	2.7%	Epidermal cyst? Dermoid cyst?	Pilomatrixoma
6	16.2%	Epidermal cyst? Dermoid cyst?	Epidermoid cyst
29	82.8%	Epidermal cyst? Dermoid cyst?	Dermoid cyst
37	100%	-	

USG: Ultrasonography MRI: Magnetic resonance imaging

In only one case, a dermoid cyst on the lateral of the right eyebrow was fistulated into the orbita through the lateral wall of the orbita. That is why preoperative USG is sufficient and CT or MRI may not be used for lesions smaller than 2 cm, localized in the frontotemporal region and especially seen in early ages. Although the initial diagnosis of dermoid cyst was established by clinical examination and USG in our patients and most of the localization was periorbital region, additional imaging studies such as CT and/or MRI were needed for differential diagnosis due to the inability to palpate these masses superficially. Regarding the treatment algorithm described by Chang et al., (3) for frontotemporal dermoid cysts in adult patients and approach to orbitofascial dermoids in pediatric population described by Bartlett et al., (6) we evaluated our patient population, size of mass and localization, then we established the examination and treatment algorithm shown in Table 3.

Although a congenital intracranial frontotemporal dermoid cyst may appear clinically as a cutaneous fistula in the first stage, intracranial extension and cutaneous sinus tract formation are rare in these dermoid cysts (12). Dermoid cysts in the scalp usually adhere to the periosteum and the normal diameter of the lesions is 1-4 cm.

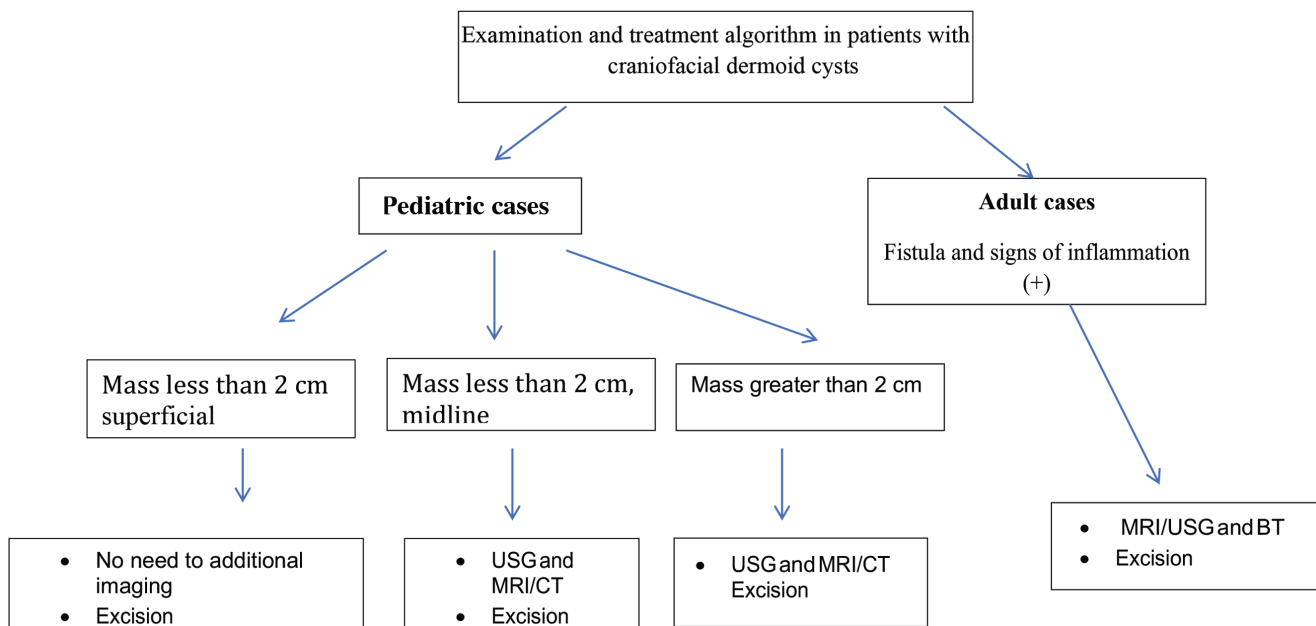
Dermoid cysts are rare in the head and neck region, but they should be included in the differential diagnosis of all nodular and cystic lesions in this region in infants and children. An intraoral nodular lesion or tongue tumor may be a dermoid cyst. A giant dermoid cyst in the neck can mimic the cystic hygroma

and MRI is required for differentiation (13).

Although dermoid cyst was one of the initial diagnoses according to preoperative imaging reports in eight patients in our study, the final pathology results were not dermoid cysts. The pathology of these patients was reported as epidermoid cyst, juvenile hemangioma or pilomatrixoma. This shows that the gold standard in the diagnosis is the pathology. Trichilemmal cysts, pilomatrixomas, hemangiomas or epidermal cysts may be similar to dermoid cysts on imaging. Therefore, the most reliable way to diagnose and understand how deeply the lesion extends is to show the lesion during the operation and total excision of the cyst tissue. In addition, in contrast to epidermal inclusion cysts, dermoid cysts in the skin are covered with an epidermis with various epidermal extensions. As a rule, these extensions are fully matured. Hair follicles containing hairs entering the lumen of the cyst are often found. The dermis of the dermoid cysts usually contains sebaceous glands, eccrine glands, and apocrine glands in many patients. Surgical excision is the preferred treatment for cyst in any localization. In order to prevent recurrence, the total removal of the dermoid cyst is necessary so that no residual cyst tissue is left behind. In our study, no recurrence was observed in any patient.

Although the treatment of dermoid cysts is surgical, surgical planning should be performed after the physical examination and completion of radiological examination. Treatment should not be delayed as the lesion may cause psychological and social problems especially in children (14). Treatment is surgical

Table 3. Treatment algorithm



excision prior to rupture. The surgical procedure is determined by the extension of the mass and the age of the patient. There are many surgical approaches described in the literature. Some of these approaches are open septorhinoplasty, bi-orbitofrontal nasal craniotomy, anterior craniotomy with lateral nasal flap and total excision of the lesion with gull wing incisions (15, 16). There are many options described in the literature for repair of defects in the bone, including autogenous bone, cartilage and dermofat graft, alloplastic materials and allogenic grafts (15).

CONCLUSION

Dermoid cysts are excised not only for elimination of poor cosmetic appearance, but also for the prevention of possible discharge and infection, for definite pathological diagnosis and for prevention of secondary bone changes. It is important not to delay treatment because it may cause psychological and social problems in children and may cause bone erosion and defects in older ages.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Ç., İ.Ü., Ö.Ö.M., Concept: Ö.Ç., İ.Ü., A.E.Ş., Ö.Ö.M., Design: Ö.Ç., İ.Ü., A.E.Ş., Ö.Ö.M., Data Collection or Processing: İ.Ü., A.A., A.E.Ş., Ö.Ö.M., Analysis or Interpretation: A.A., İ.Ü., Ö.Ö.M., Literature Search: A.A., Ö.Ö.M., Writing: Ö.Ç., A.A., Ö.Ö.M.

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Serum Neuron Specific Enolase and S-100B Levels in Hemodialysis and Peritoneal Dialysis Patients

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Abstract

Objective: Neuron-specific enolase (NSE) and S-100B are brain-derived proteins, and their levels increase in brain injury. The aim of the study was to determine serum S-100B and NSE levels in patients with end-stage renal disease undergoing hemodialysis (HD) and peritoneal dialysis (PD) and to demonstrate how these levels were affected by the type of dialysis applied.

Methods: The study group consisted of age- and gender-matched 20 patients undergoing HD, 26 patients undergoing continuous ambulatory PD (CAPD) and 21 healthy controls. Blood samples were obtained before and after dialysis in the HD patient group, and fasting blood samples were obtained in the CAPD and control groups. The routine biochemical parameters were measured within two hours from all serum samples. The remaining serum samples were stored at -80 °C until the day of analysis of the S-100B and NSE assays. Serum S-100B and NSE levels were measured by chemiluminescence immunoassay method. Routine biochemistry tests were measured by colorimetric method using a biochemistry analyzer.

Results: Serum S-100B (0.11±0.06 ng/mL in HD, 0.13±0.09 ng/mL in CAPD and 0.05±0.03 ng/mL in controls) and NSE (12.7±5.99 ng/mL in HD, 9.26±5.52 ng/mL in CAPD and 6.82±2.36 ng/mL in controls) levels were higher in HD and CAPD groups compared to controls. S-100B and NSE levels were higher after HD compared to before HD (p<0.001). There was a weak but significant correlation between S-100B and NSE levels (r=0.290; p=0.006).

Conclusion: In this study, serum S-100B and NSE levels were found to be high in patients undergoing HD and PD. Serum S-100B and NSE concentrations were higher in HD and CAPD patients. Increased S-100B and NSE levels may be associated with cerebrovascular events in patients with chronic renal failure. They may also be important markers for the determination of cerebrovascular events.

Keywords: Brain damage, end stage renal failure, hemodialysis, neuron-specific enolase, peritoneal dialysis, S-100B

INTRODUCTION

Neuron-specific enolase (NSE) and S-100B are specific brain-derived proteins that have recently gained importance as neurochemical markers (1). Serum concentrations of these analytes increase after traumatic brain injury and clinical conditions that result in brain injury, such as cardiac arrest and cardiopulmonary bypass surgery (2, 3). S-100B is a calcium-

binding protein, approximately 21 kDa in weight and composed of subunits A and B. Subunit B is synthesized mainly by astroglial and microglial cells and is highly specific for the central neurological system (4, 5). The half-life of S-100B in the serum is reported to be approximately two hours, and it is metabolized and excreted by the kidneys. Its concentrations are normally undetectable in serum samples, but can reach measurable levels



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following certain clinical conditions such as stroke, subarachnoid hemorrhage, head trauma, and extracorporeal circulation (6-8).

NSE is a dimeric isoenzyme of the glycolytic enzyme enolase that is approximately 78 kDa in weight and has a biological half-life of about 24 hours. It is highly localized in neurons and neuroendocrine cells, and constitutes 1.5% of soluble proteins in brain tissue (9). When brain tissues are injured, NSE diffuse into cerebrospinal fluid (CSF) and systemic circulation (1, 10). Recent studies have suggested that increased NSE concentrations in serum and CSF can be used as a sensitive and quantitative marker for parenchymal damage in brain tissue, cerebral infarction and intracerebral hemorrhage (9, 11).

Chronic renal disease is defined as an irreversible and progressive decrease (<60 mL/min/1.73 m²) in the glomerular filtration rate (GFR). When chronic and progressive deterioration reaches an advanced stage, it is called chronic renal failure (CRF). CRF is associated with severe disorders in the fluid and electrolytes balance, as well as in metabolic-endocrine functions. It is well known that decreased GFR is a risk factor for cerebrovascular and cardiovascular diseases. Cerebrovascular diseases are considered as one of the most important causes of higher morbidity and mortality in patients with end-stage renal disease (ESRD). It has been reported that there is a relationship between ESRD and several cerebral pathologies, including stroke, cerebral microvascular disease, silent lacunar infarct, white matter lesions and cerebral microvascular hemorrhages (12).

Controlling these risk factors plays a key role in the prevention of cerebral diseases and improving the quality of life of patients with ESRD. Magnetic resonance imaging (MRI) is still the most valuable diagnostic tool and is commonly used in the diagnosis of cerebrovascular diseases in these patients. As neurochemical markers, serum S-100B and NSE can be useful for early diagnosis of brain damage.

The purpose of this study was to determine serum NSE and S-100B levels in patients undergoing hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD), to compare these values with the control group, and to assess these neurochemical markers before and after a single HD session.

METHODS

Subjects

Twenty patients who underwent HD and 26 patients who underwent CAPD were included in the study. Twenty-one age- and gender-matched healthy controls without any systemic disease such as hypertension, chronic renal disease,

diabetes mellitus, cardiovascular or neurovascular disease were selected for the study. The study was approved by the Ethics Committee of Ankara Hospital (Approval no: 3020) in accordance with the regulations of the Ministry of Health. All patients were informed about the study procedures before being included.

Blood Sampling and Biochemical Analysis

Fasting venous blood samples were obtained from the patients before and after a HD session, while only fasting blood samples were obtained from the CAPD group and controls. Blood samples were drawn into evacuated serum separator tubes containing clot activator (SST Vacutainer®, Becton Dickinson). All blood samples were centrifuged at 1500 g for 10 minutes. Sera were separated and used for routine biochemical testing within two hours. The remaining serum samples were stored at -80 °C until the day of analysis for S-100B and NSE assays.

Serum glucose, urea, creatinine (Cre), uric acid (UA), total protein (TP), albumin (Alb), sodium (Na) and potassium (K) levels were measured with original reagent using Olympus AU 2700 analyzer (Mihsima Olympus Co. Ltd. JAPAN).

S-100B and NSE Procedure

Serum S-100B and NSE measurements were conducted using immunochemistry (Liaison® Sangtec 100, DiaSorin AB Bromma, Sweden). The minimal detection concentration was 0.02 ng/mL for S-100B and 0.04ng/mL for NSE. The intra-assay coefficient of variation (CV) was 3.7% for S-100B and 0.9% for NSE. The inter-assay CVs for S100-B and NSE were 5.7% and 5.3%, respectively.

Dialysis Procedure

All patients underwent HD three times a week for four hours per day, using a synthetic low-flux hollow-fiber filter (polysulfone membrane) (surface area 1.25 m²), with an average blood flow rate of 200-300 mL/min, and a dialysate flow rate of approximately 500 mL/min during the HD procedure. For peritoneal dialysis patients, CAPD involved four or five dwells per day of 2-2.5 liters per dwell.

Statistical Analysis

Descriptive statistics were used to analyze the data. Kolmogorov-Smirnov test was used for normality testing of the data. Differences between groups were analyzed using the Mann-Whitney U test. Spearman correlation was used to evaluate the association between variables. Pre- and post-HD values were compared using the Wilcoxon sign test. $P<0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS version 15.0.

RESULTS

Demographic data and biochemical test results are given in Table 1 and Table 2, respectively. Serum S-100B and NSE levels

Table 1. Demographic data of control and patient groups			
Variables	Control (n=21)	CAPD (n=26)	HD (n=20)
Gender			
Female (%)	9 (43%)	12 (46%)	9 (45%)
Male (%)	12 (57%)	14 (54%)	11 (55%)
Age, year (mean ± SD)	47.9±8.5	46.8±13.3	49.37±15.17
Body mass index, kg/m ² (mean ± SD)	27.7±3.7	25.35±5.2	22.58±3.2
Dialysis duration, years			
<1	-	4	5
1-5	-	17	10
5-10	-	5	5
Smoking (%)	4 (19%)	6 (23%)	2 (10%)
Diabetes mellitus (%)	-	6 (23%)	5 (25%)
Bone disease (%)	-	3 (12%)	4 (20%)
Cardiovascular disease (%)	-	2 (8%)	1 (5%)
Hypertension (%)	2	12 (46%)	14 (70%)
Dyslipidemia (%)	3	3 (12%)	8 (40%)
Thyroid disease (%)	2	3 (12%)	-
Family history (%)	-	1 (4%)	3 (15%)
Drugs used (%)			
Antilipidemic drugs	-	3 (12%)	8 (40%)
Antihypertensive drugs	-	21(81%)	14 (70%)
-Beta blockers	-	3 (12%)	2 (10%)
-ACE inhibitors	-	4 (19%)	6 (30%)
-Angiotensin II receptor blockers	-	5 (13%)	2 (10%)
-Calcium channel blockers	-	9 (35%)	6 (30%)
-Adrenergic receptor blockers	-	4 (13%)	-
Insulin	-	6 (23%)	5 (25%)
Folic acids and derivatives	-	13(50%)	20 (100%)
Drugs containing iron	-	10 (38%)	20 (100%)
Phosphate chelators	-	24 (92%)	20 (100%)
Vitamin D analogues	-	24 (92%)	20 (100%)
Erythropoietin analogues	-	5 (9%)	20 (100%)
Antiaggregant drugs	-	1 (4%)	-
Aspirin	-	2 (8%)	-
Tricyclic antidepressants	-	2 (8%)	-
T3 agonists	-	2(8%)	-

CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis, SD: Standard deviation

are given in Table 3. Serum S-100B and NSE levels were higher in HD group than in the control group (p=0.001, p=0.002, respectively). Serum S-100B and NSE levels were higher in CAPD group than in the control group (p=0.002, p=0.009, respectively). Serum S-100B and NSE levels were significantly different between CAPD and HD groups (p=0.023, p<0.001, respectively) (Table 3). There was a significant positive correlation between S-100B and NSE levels (r=0.290; p=0.006). S-100B and NSE levels were also significantly higher following a single HD session (p<0.001) (Table 4). S-100B and NSE results are shown in Figure 1.

DISCUSSION

The dialysis process may affect several biochemical factors. While many of these changes are beneficial, others can be harmful and increase the severity of the disease.

In the current study, both S-100B and NSE levels were found to be increased in patients undergoing HD and CAPD. When we evaluated the difference between the dialysis types, we found

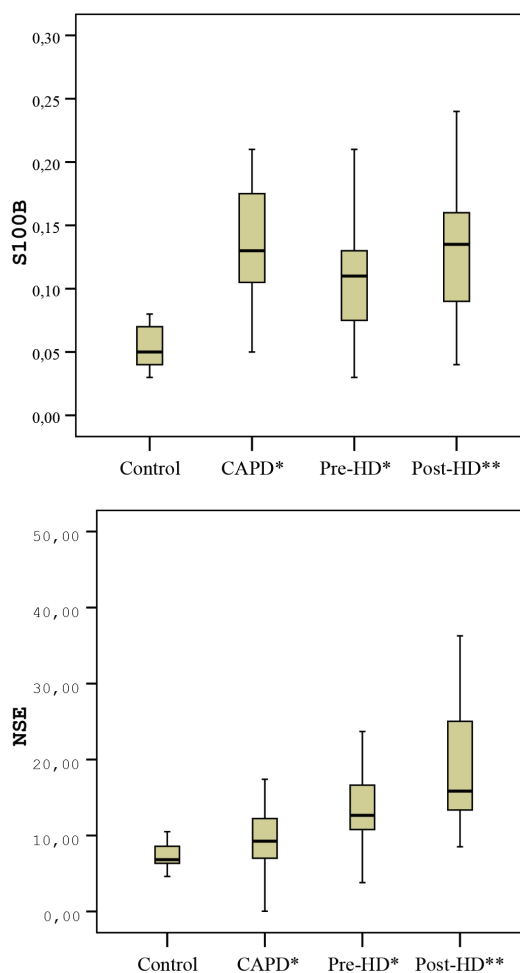


Figure 1. Serum S-100B and NSE levels in the patient and control groups CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis

that serum S-100B levels were higher and NSE levels were lower in the CAPD group than in the HD group. The kidneys normally metabolize both S-100B and NSE; therefore, in renal failure, serum levels may be expected to be higher due to decreased renal clearance. Considering the relationship between chronic renal disease and cerebrovascular disorders in these patients, increasing levels of serum S-100B and NSE may be associated with neurological tissue injury.

In this study, we also evaluated the HD effect and found that both serum S-100B and NSE levels were higher in post-HD compared to pre-HD. This could be the result of the hemodilution effect that occurs normally prior to HD and partial hemoconcentration due to dialysis therapy. Another factor contributing to higher levels following HD could be the insufficient permeability of the synthetic hollow-fiber membrane to the S-100B and NSE proteins that could result in ineffective removal. However, there is no study investigating the effect of dialysis on serum S-100B and NSE levels in the literature..

Cerebrovascular diseases are one of the most common reasons for high morbidity and mortality in patients with ESRD (1, 13). The early diagnosis of cerebrovascular disease is important to improve the prognosis and quality of life of these patients. In a previous study, Ikram et al., (14) observed that there was a relationship between decreased GFR levels and the findings in MRI, including cerebral microvascular lesions. Several other studies have reported that decreased GFR is related to an increased prevalence of subclinical lacunar cerebral infarcts detected using MRI (15, 16). In another study, decreased GFR was found to be associated with silent cerebral infarcts (17). Kim et al., (18) investigated the association between depression symptoms and serum S-100B concentrations and found that S-100B levels increased in ESRD due to glial pathology and dysfunction of the blood brain barrier. According to these previous studies, we can say that varying degrees of reduction in GFR levels are associated with cerebral pathologies in patients with chronic renal disease. In the diagnosis of cerebrovascular diseases, the measurement of serum S-100B and NSE provides significant advantage since it

Table 2. The measured biochemical parameter levels in the control and patient groups

Parameters (measuring units)	Control (n=21) M (IQR)	CAPD (n=26) M (IQR)	p*	HD (n=20) M (IQR)	p*
Glucose (mmol/L)	5.2 (1.6)	7.2 (4.7)	<0.001	6.9 (6.7)	<0.001
Urea (mmol/L)	10.6 (3.2)	40.2 (12.4)	<0.001	46.7 (10.2)	<0.001
Creatinine (µmol/L)	88 (18)	778 (239)	<0.001	787 (265)	<0.001
Uric Acid (mmol/L)	0.29 (0.06)	0.34 (0.07)	0.042	0.33 (0.06)	0.042
Total protein (g/L)	69 (5)	67 (9)	0.062	68 (6)	0.070
Albumin (g/L)	42 (4)	37 (4)	0.001	36 (4)	0.001
Na (mmol/L)	139.3 (2.5)	138.6 (3.4)	0.125	136.0 (5.0)	0.102
K (mmol/L)	4.4 (0.4)	4.3 (0.5)	0.086	5.4 (0.8)	0.001
Systolic blood pressure (mmHg)	115 (12)	132 (19)	0.001	142 (19)	0.001
Diastolic blood pressure (mmHg)	75 (6)	82 (9)	0.001	80 (11)	0.001

*p value; comparing control and study groups. CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis, M: Median, IQR: Inter quartile range

Table 3. Comparison of serum S-100B and NSE levels in the control and patient groups

Parameters (measuring units)	Control (n=21) M (IQR)	CAPD (n=26) M (IQR)	p*	HD (n=20) M (IQR)	p*	p**
S-100B (ng/mL)	0.05 (0.03)	0.13 (0.09)	0.002	0.11 (0.06)	0.001	0.023
NSE (ng/mL)	6.82 (2.36)	9.26 (5.52)	0.009	12.7 (5.99)	0.002	<0.001

*p value; comparing control and study groups. **p value; comparing CAPD and HD. CAPD: Continuous ambulatory peritoneal dialysis, HD: Hemodialysis, M: Median, IQR: Inter quartile range

Table 4. Comparison of serum S-100B and NSE levels before and after hemodialysis

Parameters (measuring units)	Before (n=20) M (IQR)	After (n=20) M (IQR)	p*
S-100B (ng/mL)	0.11 (0.06)	0.13 (0.07)	<0.001
NSE (ng/mL)	12.7 (5.99)	15.84 (11.72)	<0.001

*p value; comparing before and after hemodialysis, M: Median, IQR: Inter quartile range

is easy to perform and non-invasive; however, there is no study in literature investigating S-100B and NSE concentrations in patients with ESRD, and the present study is the first in this field.

CONCLUSION

In this study, we determined that serum S-100B and NSE levels increased in patients undergoing HD and CAPD therapy compared to controls. Therefore, these markers might be valuable in determining the possible risk of a cerebrovascular event in patients with chronic renal disease. Nevertheless, one of the limitations of this study was that further studies are needed to compare serum S-100B and NSE levels with MRI findings in patients with CRF. Another limitation was that study cohort was relatively small.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Hospital (approval no: 3020) in accordance with the regulations of the Ministry of Health.

Informed Consent: All patients were informed about the study procedures before being included.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ş., A.A., M.D., D.Y., Concept: M.A., O.Ö., M.Ş., D.Y., Design: M.A., O.Ö., M.Ş., Data Collection or Processing: M.A., O.Ö., M.F.A., M.Ş., Analysis or Interpretation: M.A., D.Y., Literature Search: M.A., O.Ö., M.F.A., Writing: M.A., O.Ö., D.Y.

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

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The Relationship Between Causative Microorganisms and Airway Obstruction in Patients with COPD Exacerbation

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Abstract

Objective: Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease. Exacerbations and comorbidities contribute to the severity of the disease. In our study, we aimed to evaluate the relationship between causative microorganisms and airway obstruction in patients hospitalized for COPD exacerbation.

Methods: Sputum and blood cultures of 75 patients, who were admitted to Nevşehir State Hospital Chest Diseases Unit between January 2015 and January 2016 and who were diagnosed as COPD exacerbation, were analyzed retrospectively. The relationship between microorganisms in sputum culture and airway obstruction was evaluated. Forced expiratory volume in one second (FEV₁) value was used to evaluate airway obstruction.

Results: Of the 75 patients evaluated in our study, 45 (60%) were male and 30 (40%) were female. The mean age was 61.2 years. Isolated microorganisms were as follows: *H. influenzae* in 12 (16%) patients, *S. pneumoniae* in nine (12%) patients, *M. catarrhalis* in six (8%) patients, *P. aeruginosa* in four (5.3%) patients, *E. coli* in three (4%) patients, *K. pneumoniae* in three (4%) patients, and methicillin-sensitive *S. aureus* in one (1.3%) patient. No statistically significant difference was found between the microorganisms in terms of airway obstruction ($p>0.05$).

Conclusion: We did not find a correlation between the causative microorganism and airway obstruction in patients hospitalized for COPD exacerbation.

Keywords: COPD exacerbation, sputum culture, airway obstruction, FEV₁

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by the chronic inflammatory response of the airways and lungs against harmful gases and particles, leading to a progressive limitation of airflow. Exacerbations and comorbidities that occur during the course of the disease cause an increase in the severity of the disease (1).

Exacerbation of COPD has been described as a condition characterized by acute deterioration of the patient's respiratory tract symptoms leading to drug change (1). There is a loss of pulmonary functions due to exacerbations, which leads to impaired quality of life and an increase in morbidity and mortality.

The etiology of COPD exacerbations consists of tracheobronchial infections (50-70%) and air pollution (10%), and the etiology cannot be detected in about 30% of exacerbations. In patients with COPD, exacerbations should be prevented and treated in order to prevent disease progression and to maintain quality of life.

In our study, we aimed to evaluate tracheobronchial infectious agents in sputum culture, and the relationship between cautious microorganisms and airway obstruction in patients hospitalized for COPD exacerbation.

METHODS

Seventy-five patients, who were admitted to Nevşehir State Hospital Chest Diseases Unit with COPD exacerbation between January 2015 and January 2016, were evaluated retrospectively.



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Patients who were not treated with antibiotics one month before admission were evaluated. Patients with cystic fibrosis, asthma and bronchiectasis were excluded from the study.

Sputum and blood cultures that were obtained for the isolation of microbiological agent causing acute exacerbation of COPD were examined. Sputum samples with polymorphonuclear leukocyte count >25 and mouth epithelial cells <10 in all areas were evaluated. Pulmonary function tests performed in the stable period of three months before the acute exacerbation were evaluated. Forced expiratory volume in 1 second (FEV₁) value was used to evaluate airway obstruction. Patients with positive sputum culture were divided into two groups according to FEV₁ (FEV₁ >50% and FEV₁ <50%).

Statistical Analysis

Statistical analyzes were performed using IBM SPSS Statistics 22 software. Mean and standard deviation was used for numerical data when evaluating the study data. Frequency distributions were calculated for comorbidities and isolated microorganisms from sputum cultures. The chi-square test was used to evaluate the relationship between FEV₁ value and the causative microorganism.

RESULTS

Of the 105 patients evaluated in our study, 30 patients were not included in the study because of antibiotic use up to one month before hospitalization and having comorbidities such as asthma and bronchiectasis. Of the 75 patients evaluated in our study, 45 (60%) were male and 30 (40%) were female. In our study, the mean age of patients was 61.2±16.3 (range, 40-85).

The complaints of the patients were as follows: increased dyspnea in 65 (86%) patients, cough in 60 (80%) patients, increased sputum in 55 (73%) patients, and change in sputum color in 36 (48%) patients. While 50 (66%) patients continued smoking, 25 (33%) had quit smoking.

The mean FEV₁ was 1.35±0.75 L (47.7%±20.68), FEV₁/forced vital capacity (FVC) was 50.4%±15.2, and FVC was 1.79±0.79 L (56.81±17.45).

Twenty-eight (37%) of the 75 patients had hypertension, 24 (32%) had diabetes mellitus, 18 (24%) had congestive heart failure, 12 (16%) had atherosclerotic heart disease, four (5%) had lung cancer, four (5%) had obstructive sleep apnea and three (4%) had depression (Table 1).

Isolated microorganisms were as follows: *H. influenzae* in 12 (16%) patients, *S. pneumoniae* in nine (12%) patients, *M. catarrhalis* in

six (8%) patients, *P. aeruginosae* in four (5.3%) patients, *E. coli* in three (4%) patients, *K. pneumoniae* in three (4%) patients, and methicillin-sensitive *S. aureus* in one (1.3%) patient. Normal throat flora elements were observed in 37 (49.3%) patients (Table 2).

Positivity was detected in only four of the blood cultures obtained during hospitalization of the patients. Isolated microorganisms were *S. pneumoniae* in one (1.3%) patient, *E. coli* in one (1.3%) patient, *H. influenzae* in one (1.3%) patient and *K. pneumoniae* in one (1.3%) patient.

FEV₁ was >50% in 18 (47%) patients and <50% in 20 (53%) patients with positive sputum culture (Table 3).

As they are the most common isolated microorganisms in acute bacterial COPD exacerbations, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* growth in patients with FEV₁ >50% were compared with the group with FEV₁ <50% (group with severe airway obstruction). There was no statistically significant difference between the two groups in terms of sample distribution (p>0.05).

Patients with FEV₁ >50% and <50% were compared in terms of gram (+) and gram (-) bacteria growth. There was no statistically significant difference between the two groups in terms of gram (+) and gram (-) bacteria growth (p>0.05).

Comorbidity	Number	%
Hypertension	28	37
Diabetes mellitus	24	32
Congestive heart failure	18	24
Atherosclerotic heart disease	12	16
Lung cancer	4	5
Obstructive sleep apnea	4	5
Depression	3	4

Bacteria	Number	%
<i>H. influenzae</i>	12	16
<i>S. pneumoniae</i>	9	12
<i>M. catarrhalis</i>	6	8
<i>P. aeruginosae</i>	4	5.3
<i>E. coli</i>	3	4
<i>K. pneumoniae</i>	3	4
<i>S. aureus</i> (methicillin-sensitive)	1	1.3
Normal throat flora elements	37	49.3
Total	75	100

DISCUSSION

Exacerbation of COPD is characterized by acute deterioration of the patient's respiratory tract symptoms leading to drug change (1). Exacerbations have negative effects on morbidity and mortality. As the disease progresses, the frequency and severity of exacerbations increase and the quality of life of COPD patients is further reduced.

The etiology of COPD exacerbations consists of tracheobronchial infections (bacterial agents 40-50%, viral agents 30-40%, atypical bacterial agents 5-10%) and air pollution (10%), and the etiology cannot be detected in about 30% of exacerbations (2). Respiratory pathogens can be detected in the respiratory tract in the stable period of the disease, so the role of infectious agents in exacerbations is controversial. In bronchoscopic studies, it was observed that approximately half of the patients had higher concentrations of bacteria in the lower respiratory tract during exacerbation than the stable period of the disease (3). In our study, we detected 50.7% bacterial infection in the etiology of exacerbations.

In a study to determine the indication for antibiotics in COPD exacerbations, the basic criterion for antibiotic indication was found to be sputum purulence. In this study, 86 patients with positive sputum culture were evaluated and 73 of them had purulent sputum (sensitivity 84-94%, specificity 77-84%) (4). In our study, sputum purulence was increased in 36 (48%) patients. According to the Committee on Publication Ethics study, it is recommended that antibiotics should be given in case of visualization of bacteria with gram staining, decrease in respiratory function, and two or more exacerbation history within last year, and antibiotic treatment is not recommended in the absence of any of these criteria (absence of all these criteria has 100% negative predictive value) (5).

The most frequently causative bacterial agents responsible for exacerbations are *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*. Enteric gram (-) bacteria and *P. aeruginosa* are increasingly isolated in patients with severe airway obstruction, hypoxemia, malnutrition, comorbidity, frequent hospitalization and antibiotic use (6, 7, 8). In our study, similar to literature, the most frequently isolated infectious agents were *H. influenzae* in 12 (16%) patients, *S. pneumoniae* in nine (12%) patients and *M. catarrhalis* in six (8%) patients. In recent years, studies that are supported by serological diagnostic methods reported that *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* might be responsible for a significant proportion of COPD exacerbations (4-34%), and atypical bacteria were not detected in studies using polymerase chain reaction (9).

Viruses are responsible for 15-40% of COPD exacerbations caused by infectious causes and a significant proportion of these infections are found together with bacterial infections (10, 11). In a study by Seemungal et al., (12) they stated that 64% of patients with COPD exacerbations had common cold 18 days before exacerbation and that rhinoviruses were the most common respiratory tract virus with a rate of 58%. In our study, no growth was detected in sputum culture of 37 (49.3%) patients and we think that atypical bacteria, viruses or non-infectious causes may cause exacerbation in these patients.

Eller et al. (13) reported that the microorganisms isolated in the exacerbations of infective COPD might change with the degree of impairment of pulmonary function. They reported that most of the microorganisms isolated in patients with FEV₁ values >50% were *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, and that gram-negative microorganisms such as *Enterobacteriaceae* and *Pseudomonas* spp. were more common in cases with severe airway obstruction with a FEV₁ <35%. Miravittles et al., (14) found higher rates of *Pseudomonas* spp. and *H. influenzae* in patients with COPD exacerbation and FEV₁ <50%. In our study, we found no significant difference in the distribution of causative microorganisms in cases with severe airway obstruction (FEV₁ <50%) and FEV₁ >50%. We believe that the retrospective nature of our study and the low number of causative microorganisms in the sputum culture may be effective on this result.

CONCLUSION

We aimed to evaluate the relationship between tracheobronchial infectious agents and airway obstruction in patients with COPD exacerbation. We did not find a relationship between the

Causative microorganism	FEV ₁ >50%	FEV ₁ <50%	Total	p
<i>H. influenzae</i>	5 (42%)	7 (58%)	12	0.148
<i>S. pneumoniae</i>	5 (55.5%)	4 (44.5%)	9	0.164
<i>M. catarrhalis</i>	3 (50%)	3 (50%)	6	0.213
<i>E. coli</i>	1 (33.3%)	2 (66.6%)	3	0.394
<i>K. pneumoniae</i>	1 (33.3%)	2 (66.6%)	3	0.394
<i>P. aeruginosae</i>	2 (50%)	2 (50%)	4	0.369
<i>S. aureus</i> (methicillin-sensitive)	1 (100%)	-	1	0.512
Total	18 (47%)	20 (53%)	38	0.102

p>0.05, FEV₁: Forced expiratory volume in 1

distribution of cautious microorganisms and airway obstruction in COPD exacerbations. We believe that this is due to the low number of patients with isolated causative agents.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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

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Recurrence Rate of Primary Superficial Bladder Tumors (Uroepithelial Tumors) at 2-Year Follow-up and Its Relationship with Smoking

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Abstract

Objective: In this study, we investigated recurrence rates of primary superficial bladder tumors (uroepithelial tumors) at 2-year follow-up and its relationship with smoking.

Methods: We retrospectively reviewed the data of 542 patients who underwent transurethral resection of bladder tumor for primary bladder tumor between 2006 and 2011 in our clinic. Our study included 105 patients with superficial bladder tumors, who had 2-year follow-up and ≤ 3 cm tumors in up to 3 foci. Data regarding age, gender, smoking, tumor stage, tumor grade, tumor size, number of tumors, postoperative early chemotherapy, induction bacillus Calmette-Guérin (BCG), adjuvant chemotherapy, recurrence within 2 years and time to recurrence were analyzed. Exposure to cigarette smoking was grouped as ≥ 20 , 30, 40 pack years.

Results: Recurrence was detected in 23 patients (21.9%). There were 94 (89.5%) smokers and 11 (10.5%) non-smokers. In multivariate analysis using logistic regression, T category, 6-week intravesical BCG, < 60 years of age and ≥ 20 pack year cigarette exposure were found to be effective parameters on recurrence ($p=0.022$, $p=0.042$, $p=0.011$, $p=0.042$, respectively).

Conclusion: Multivariate analysis of our study revealed that ≥ 20 pack years of smoking shortened recurrence-free survival. Evaluation of long-term results of existing therapies and development of new treatment modalities are needed to better identify risk factors for recurrence of bladder tumors.

Keywords: Bladder cancer, smoking, recurrence

INTRODUCTION

According to the statistics, transitional cell carcinoma of the bladder is the second most common urological cancer after prostate cancer, and is an important cause of mortality and morbidity. In developed countries, it ranks 4th in men and 9th in women. Although there are many factors involved in the etiology of bladder cancer, the most important factor is smoking (1).

Most (90%) of the bladder cancers are urothelial cancers (2). Approximately 80% of urothelial cancers of the bladder are limited to mucosa and submucosa at the time of diagnosis; therefore, they are named as “superficial bladder tumor” or

“non-muscle-invasive bladder cancer” (2, 3). Although tumor can be controlled initially, it has the feature of frequent recurrence. In the first 3-month follow-up, recurrence rate ranges from 0% to 36% in single tumors and 7% to 75% in multiple tumors (4). Chen et al. (5) found that smoking was an independent risk factor for shorter recurrence-free survival in patients with T1 category, high-grade and multiple tumors who continued to smoke following bladder tumor diagnosis and primary treatment.

The aim of this study was to determine the relationship between the recurrence of primary superficial bladder tumors (uroepithelial tumors) with age, gender, tumor stage, tumor grade,



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number of tumors, postoperative early chemotherapy, repeat-urethral resection of bladder tumor (re-TURBT), induction bacillus Calmette-Guérin (BCG), adjuvant chemotherapy and smoking.

METHODS

The data of 542 patients who underwent TURBT due to primary bladder tumor between 2006 and 2011 were evaluated retrospectively. Our study included 105 patients with superficial bladder tumors, who had 2-year follow-up and ≤ 3 cm tumors in up to 3 foci. Tumor size measurement was calculated based on the width of the TUR loop. Data regarding age, gender, smoking, tumor stage, tumor grade, tumor size, number of tumors, postoperative early chemotherapy, induction BCG, adjuvant chemotherapy, recurrence within 2 years and time to recurrence were analyzed. Exposure to cigarette smoking was grouped as ≥ 20 , 30, 40 pack years.

Following being informed about the disease and signing the informed consent form, the patients who were diagnosed as primary bladder tumor were operated. TURBT electroresection was performed by urology specialists. The operation was performed in the form of total resection, muscle sampling and fulguration of the tumor base.

Histopathological examinations of all patients were performed in the İzmir Atatürk Training and Research Hospital pathology laboratory. Tumors were staged according to the 2002 tumor-node-metastasis system and were classified according to the World Health Organization, International Society of Urological Pathology 2004 tumor classification system. Cystoscopy and cytology follow-ups were performed quarterly in the first 2 years and every six months later after the diagnosis of superficial bladder tumor. Re-TURBT was performed in patients with recurrence.

Statistical Analysis

Normality of the data was assessed using one sample Kolmogorov-Smirnov test, histogram, Q-Q plot and box plot graphics. Data were given as mean, standard deviation, frequency and percentage. Nominal variables were evaluated by chi-squared test with Yates' continuity correction and Fisher's exact test. Logistic regression analysis was performed to determine the parameters that may be effective on recurrence. Factors affecting recurrence-free survival were evaluated by Cox regression analysis. Survival analysis was performed by Kaplan-Meier method. A two-tailed $p < 0.05$ was accepted as statistically significant. Analysis was performed using SPSS 16.0 software program.

RESULTS

The mean age of the patients was 62.5 (± 12.2) years. The number of smokers was 94 (89.5%) and 11 (10.5%) were non-smokers. Eighty-nine (84.8%) patients were male and 16 (15.2%) were female. Of the 105 patients, 23 had recurrence (21.9%). The pathological findings of 72 patients (68.6%) were category Ta and 33 patients (31.4%) were category T1. These tumors were low-grade in 72 patients (68.6%) and high-grade in 33 patients (31.4%). No simultaneous carcinoma-in-situ was reported in any of the patients. Single tumor was detected in 75 patients (71.4%), while 30 patients (28.6%) had tumors in 2 or 3 foci (Table 1).

Postoperative early intravesical chemotherapy was performed in 70 patients (66.7%). The pathologies of the patients were evaluated, and 6-week intravesical chemotherapy (mitomycin-c, epirubicin) was performed in 14 patients (13.3%) and 6-week intravesical BCG was performed in 25 patients (23.8%). Re-TURBT was applied to 21 patients (20%). Deep resection with perivesical fat tissue visualization occurred in a total of 3 patients (2.9%), but no extravasation and additional complications were observed during postoperative follow-up. These patients did not receive postoperative early intravesical therapy. Only one patient had postoperative fever (1%), and no patient had any bleeding complications requiring transfusion.

In the 2-year follow-up of the patients, five of 33 patients with category T1 tumors and 18 of 72 patients with category Ta tumors had recurrence ($p=0.38$). Recurrence was observed in 15 of 72 patients with low-grade tumors and in eight of 33 patients with high-grade tumors ($p=0.89$). Recurrence was found in seven of 21 patients who had re-TURBT and 16 of 84 patients who did not undergo re-TURBT ($p=0.24$). Recurrence occurred in two of 11 non-smokers and 21 of 94 smokers ($p=0.99$). The primary pathology of two non-smokers who had recurrence was Ta low-grade and recurrence pathology was Ta low-grade, and there was no progression. Recurrence was detected in 14 of 75 patients with single tumor, and recurrence was found in nine of 30 patients with tumors in 2 or 3 foci ($p=0.31$). Recurrence was observed in 12 of 70 patients who underwent postoperative early intravesical chemotherapy and in 11 of 35 patients who did not ($p=0.16$). Recurrence was observed in four of 14 patients who underwent postoperative 6-week intravesical chemotherapy and in 19 of 91 patients who did not ($p=0.73$). Recurrence was observed in six of 25 patients who underwent postoperative 6-week intravesical BCG and in 17 of 80 patients who did not ($p=1$). When the patients were grouped according to their gender, recurrence occurred in 21 of 89 male patients and 2 of 16 female patients ($p=0.36$). When the patients were

classified as over and under age 60, 15 of 47 patients under the age of 60 had recurrence and eight of 58 patients over 60 years of age had recurrence (p=0.046). When the smoking status of the patients was divided into 20-30-40 pack/year above and below, the rate of recurrence was not statistically significant (p=0.24, p=0.91, p=1, respectively). The effects of patient characteristics, treatments and smoking (pack/year) on the recurrence were shown as separate tables (Tables 1, 2 and 3).

In multivariate analysis using logistic regression, pathologic T category, 6-week intravesical BCG, <60 years of age and ≥20 pack/year smoking parameters were found to be effective on recurrence in all patients (p=0.022, p=0.042, p=0.011 p=0.042, respectively) (Table 4).

In the survival analysis (Kaplan-Meier) in pathological T1 patients, ≥40 packs/year smoking was found to be significant on recurrence-free survival (p=0.033) (Figure 1).

When T1 patients were evaluated with Cox regression in multivariate analysis, re-TURBT and ≥40 pack/year smoking were found to be significant in recurrence-free survival (p=0.028, p=0.031, respectively) (Table 5).

	Number of patients	Recurrence +	Recurrence -	p
Gender				
Male	89	21	68	0.36*
Female	16	2	14	
Age				
<60 years of age	47	15	32	0.046**
≥60 years of age	58	8	50	
Smoking				
Smoker	94	21	73	0.99*
Non-smoker	11	2	9	
Pathological tumor stage				
Ta	72	18	54	0.38**
T1	33	5	28	
Grade				
Low-grade	72	15	57	0.89**
High-grade	33	8	25	
Number of tumors				
Single	75	14	61	0.31**
2 or 3	30	9	21	

*Fisher's exact probability test **Chi-squared test with Yates' continuity correction

	Number of patients	Recurrence +	Recurrence -	p
Re-TURBT				
Yes	21	7	14	0.24**
No	84	16	68	
Postoperative early IVCT*				
Yes	70	12	58	0.16***
No	35	11	24	
6-week IVCT*				
Yes	14	4	10	0.73**
No	91	19	72	
Induction BCG				
Yes	25	6	19	1***
No	80	17	63	

Re-TURBT: Repeat-transurethral resection of bladder tumor *IVCT: Intravesical chemotherapy, **Fisher's exact probability test, ***Chi-squared test with Yates' continuity correction

	Number of patients	Recurrence +	Recurrence -	p*
Pack year of smoking				
<20 pack year	31	4	27	0.24
≥20 pack year	74	19	55	
Pack year of smoking				
<30 pack year	56	12	44	0.91
≥30 pack year	49	11	38	
Pack year of smoking				
<40 pack year	80	18	62	1
≥40 pack year	25	5	20	

*Chi-squared test with Yates' continuity correction

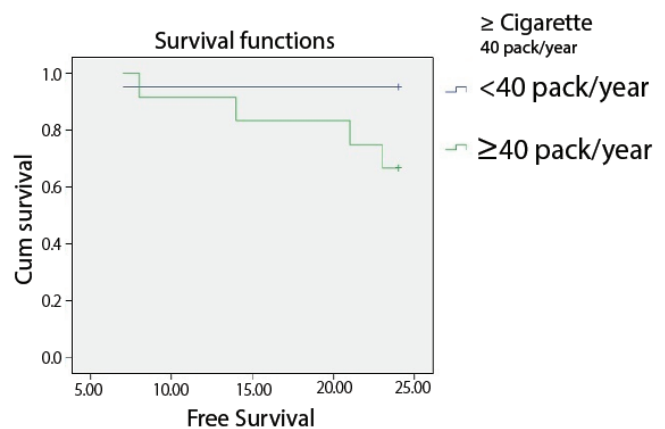


Figure 1. The effect of >40 pack/year smoking on recurrence-free survival in T1 tumors

Regarding 72 patients with Ta pathology, recurrence was observed in eight of 48 patients who received postoperative early intravesical chemotherapy and in 10 of 24 patients who did not ($p=0.043$). In the subgroup analysis, postoperative early intravesical chemotherapy in low-grade group patients was found to be statistically associated with low recurrence rates ($p=0.035$).

DISCUSSION

In the treatment of superficial bladder tumors, the target is to keep recurrence and progression rates at the lowest levels. In a study by European Organisation for Research and Treatment of Cancer (EORTC) on 2596 patients with Ta and T1 tumors with a mean follow-up of 3.9 years (maximum 14.8 years) in 2006, recurrence was observed at least once in 1240 patients (47.8%). The mean time to first recurrence was 2.7 years (6). In our study, 23 of 105 patients (21.9%) had recurrence. In our study, the recurrence rate was lower since patient group included patients with <3 cm tumor in up to 3 foci. The low number of tumors and smaller tumor size in our cohort represent low-risk group and the low recurrence rate can be explained in that way. In addition, evaluation of only the first 2 years and the majority of patients having Ta and low-grade bladder tumor were the other factors.

Smoking is the most important risk factor for bladder cancer and is thought to be responsible for approximately 50% of all patients (7, 8). Cigarette includes aromatic acid and polycyclic

aromatic hydrocarbons excreted from the kidneys. In our study, 94 (89.5%) of 105 patients were smokers. There was no statistically significant difference between the smokers and the non-smokers in terms of recurrence ($p=0.757$). When the patients were divided into ≥ 20 -30-40 pack/year smokers, there was no statistical significance in terms of recurrence (Table 3). In multivariate analysis using logistic regression, patients with ≥ 20 pack/year of smoking had more recurrence compared to patients with less smoking or no smoking ($p=0.042$). Besides, multivariate analysis using Cox regression revealed that ≥ 20 pack/year smoking decreased recurrence-free survival ($p=0.037$). Although the carcinogen effect of cigarette has not been clearly defined, it is emphasized that there is adduction and mutagenicity effect of aromatic acid on DNA (9). In a study conducted by Flesner et al., (10) the multivariate analysis in patients who continued smoking revealed that recurrence-free survival was shorter compared to the patients who quit and who were ex-smokers. The retrospective nature of our study, the limited characteristics of patients selected and the low number of patients were the main reasons for the lack of fully demonstrating the effect of smoking.

A possible outcome of this study was the extent to which smoking cessation and cessation time affected tumor recurrence. However, in our retrospective study, we determined that smoking cessation was not questioned in the follow-up of these patients, and we make great efforts to achieve smoking cessation in every patient diagnosed with and treated for bladder tumor. The fact

Table 4. The effective parameters on recurrence in multivariate analysis using logistic regression in all patients

	B	SE*	p	OR	95% CI of OR**	
					Minimum	Maximum
Re-TURBT	1.17	0.68	0.085	3.226	0.850	12.243
PoIVCT	-0.94	0.55	0.083	0.389	0.134	1.132
BCG 6	1.91	0.94	0.042#	6.779	1.074	42.787
<60 years	-1.48	0.58	0.011#	0.228	0.073	0.710
≥ 20 p-y smoking	1.41	0.69	0.042#	4.080	1.052	15.820
pT	-2.32	1.01	0.022#	0.098	0.014	0.713

*SE: Standard error, **CI: Confidence interval, OR: Odds ratio # $p<0.05$: Variables, Re-TURBT: The number of tumors, PoIVCT: Early intravesical chemotherapy postoperatively, post-operative 6-week chemotherapy, BCG 6: Bacillus Calmette-Guérin, <60 years, ≥ 20 , 30, 40 pack year of smoking (20 p-y smoking), pathologic grade, smoking, deep esection, gender, Pt: Pathological T

Table 5. The effective parameters on relapse-free survival in multivariate analysis using Cox regression in T1 patients

	B	SE*	p	OR	95% CI of OR**	
					Minimum	Maximum
Re-TURBT	2.63	1.19	0.028#	13.928	1.330	145.822
≥ 40 pack/year of smoking	2.6	1.21	0.031#	13.552	1.272	144.426

*SE: Standard error, **CI: Confidence interval, OR: Odds ratio, #: $p<0.05$

that 89.5% of the patients in our study consisted of smokers further emphasized the importance of this situation.

In studies on patient age and superficial bladder tumor characteristics, recurrence-free survival and prognosis were found to be better in young patients (11-13). In our study, recurrence occurred in 15 of 47 patients under 60 years of age and in eight of 58 patients aged 60 years and older ($p=0.026$). In addition, recurrence-free survival under the age of 60 was found to be shorter than the patients aged 60 years and older ($p=0.029$). Patients over 60 years of age had a higher rate of pathologic T1 and higher grade than those under 60 years ($p=0.015$ and $p=0.044$, respectively). However, postoperative 6-week BCG application was found to be higher in patients older than 60 years ($p=0.017$). These conflicting results with the literature can be the result of many different factors affecting the recurrence of superficial bladder tumor.

In EORTC's 2006 risk score table for recurrence and progression in superficial bladder tumors, risk and progression scores were calculated using number of tumors, tumor size, prior recurrence rate, T category, carcinoma in situ (CIS), and grade (6). Following this, Club Urológico Español de Tratamiento Oncológico (CUETO) published progression and recurrence risk factors study in 2009 in which the results of 1,062 patients who underwent BCG were compared (14). Age, gender, previous recurrence status, number of tumors, T category, CIS, and tumor grade were used as risk factors. Using this table, the risk of recurrence was found to be lower in comparison with EORTC scoring system. Progression was lower in only high-risk patients. The low risk in CUETO tables can be correlated with BCG, which is an effective treatment. Many studies are needed for molecular markers to take place in the risk tables (15, 16).

In our study, multivariate analysis was performed using logistic regression in all patients and lower recurrence rates were found with pathological T1, 6-week intravesical BCG, ≥ 60 years of age and < 20 pack/year cigarette exposure ($p=0.022$, $p=0.042$, $p=0.011$ and $p=0.042$, respectively) (Table 4). A lower rate of recurrence in patients with T1 category than Ta category indicates the efficacy of adjuvant treatments. Considering the patient group included in this study, we cannot mention the validity of the same situation for general superficial bladder tumors. As a result of the meta-analyses to be made in the coming years, it is predicted that the parameters affecting the recurrence will be defined more clearly.

In the subgroup analysis performed in our study, it was found that postoperative early intravesical chemotherapy in patients with low-grade group and Ta category was statistically significantly

associated with low recurrence rates ($p=0.021$, $p=0.035$, respectively). With early instillation, the destruction of free tumor cells within the bladder after TUR had an ablation effect on residual tumors in the resection area and the tumors that were overlooked (17, 18). A single dose of early chemotherapy being an adequate adjuvant therapy in low-risk Ta tumors has been mentioned in the 2013 European guidelines (19). Postoperative early chemotherapy should be avoided in patients with suspected perforation or requiring irrigation. Serious drug-related complications have been reported. These can be listed as peritonitis due to chemotherapeutic agent, infiltrative mass, and paralytic ileus causing colostomy and multiple organ failure (20). In our study, three patients did not undergo postoperative single-dose chemotherapy because of suspicion of deep resection and perforation. Two of these patients had recurrence in the first 2 years.

Study Limitations

In our study, the direct significance of many factors with recurrence could not be demonstrated. The retrospective nature of our study and the inclusion of a narrow patient population were the limitations of our study. We think that more significant results can be obtained with prospective multicenter randomized studies.

CONCLUSION

Eighty-nine point five percent of the bladder cancer patients included in our study were found to be smoking. Multivariate analysis showed that ≥ 20 pack/year of smoking decreased recurrence-free survival. Smoking cessation studies and providing public information are of great importance in the prevention of systemic diseases along with smoking-related bladder cancer and other cancers. It is understood that long-term (smoking cessation and have quitted it for a long time) studies are needed in order to understand how cessation of smoking and the duration of cessation affects recurrence in superficial bladder tumors. Evaluation of long-term results of current treatment modalities and development of new treatment modalities and histopathological genetic studies are needed in order to better identify risk factors affecting recurrence in bladder cancer.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.Ç., O.K., Y.Y., Concept: B.Ç., Ü.Ö., O.K., Y.Y., Design: B.Ç., Ü.Ö., Y.Y., Data Collection or Processing: B.Ç., Analysis or Interpretation: O.K., Literature Search: B.Ç., Writing: B.Ç., Ü.Ö., O.K., Y.Y.

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Comparison of Maternal Serum Soluble Fms-Like Tyrosine Kinase-1/Placental Growth Factor Ratio in Preeclamptic and Normotensive Pregnant Women

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Abstract

Objective: It has been suggested that the underlying pathology in preeclampsia is inadequate trophoblastic invasion, abnormal placentation and extensive endothelial damage. The aim of this study was to compare soluble Fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PGF) levels and sFlt-1/PGF ratio between preeclamptic and normotensive pregnant women, and to determine the increase in sFlt-1, which is an important antiangiogenic factor in the development of preeclampsia.

Methods: Following local ethics committee approval, this prospective study was carried out with 43 pregnant women, including 20 preeclamptic and 23 normotensive pregnancies, who were admitted to our clinic. The two groups were compared in terms of gestational characteristics, sFlt-1 levels, PGF levels and sFlt-1/PGF ratio.

Results: Serum sFlt-1 levels and sFlt-1/PGF ratio were higher and serum PGF levels were lower in preeclamptic women compared to the control group.

Conclusion: The sFlt-1/PGF ratio was significantly higher in preeclamptic pregnant women than in normotensive pregnant women. This higher ratio suggests that sFlt-1 has a role in the development of hypoxia and inadequate angiogenesis in preeclamptic pregnancies.

Keywords: Preeclampsia, sFlt, placental growth factor

INTRODUCTION

Preeclampsia is a multisystemic disorder characterized by hypertension accompanied by proteinuria and/or end organ damage in a normotensive woman after 20 weeks of gestation. It is seen in approximately 3-8% of pregnancies and is responsible for 18% of maternal mortality and 40% of fetal mortality worldwide (1, 2).

Despite its high mortality and morbidity, its etiology and pathophysiology are still unclear. Abnormal placentation with insufficient trophoblastic invasion and extensive endothelial damage is the main proposed pathology. Immunological intolerance, genetic abnormalities, metabolic and nutritional factors between fetoplacental tissue and maternal tissue are factors suggested in the pathogenesis (3).

The imbalance between angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PGF) and antiangiogenic factors such as Soluble Fms-like Tyrosine Kinase-1 (sFlt-1) and soluble endoglin (s-Eng) has been suggested to play a role in the pathogenesis of preeclampsia by causing endothelial dysfunction (4, 5).

sFlt-1 is over-produced in trophoblastic tissues of pregnant women who will encounter preeclampsia. sFlt-1 is a variant of the Flt-1 receptor for PGF and VEGF. The increase in maternal serum sFlt-1 levels affects the free PGF and VEGF in the circulation and causes endothelial dysfunction. Although not yet clearly explained, it is thought that the hypoxia caused by the deterioration of placental perfusion leads to over-production of antiangiogenic proteins in the placenta (6).



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The aim of this study was to determine the sFlt-1/PGF ratio in preeclampsia, which is an important cause of maternal morbidity and mortality.

METHODS

This study was planned following approval from Clinical Research Ethics Committee of İstanbul Okmeydanı Training and Research Hospital, University of Health Sciences. Forty-three pregnant women, including 20 preeclamptic and 23 normotensive women, who were admitted to department of obstetrics and gynecology between September 2016 and April 2017 and who consented, were included in the study. The patients were between the ages of 15-44 and had singleton pregnancies.

Blood pressure in each patient was measured from the brachial artery using standard measurement technique, in sitting position and the cuff at the heart level.

Ten mL of blood samples were drawn from the antecubital brachial vein of the patient and control group by using Vacutainer blood collection tube. The biochemistry tube was centrifuged at 3000 xg for 10 minutes. The obtained serum was stored at -80°C to be used on the day of analysis. On the day of the analysis, the eppendorf tubes were brought to room temperature, and the frozen sera were melted. The measurement of serum human sFlt-1 and PGF were performed by ELISA in the Biochemistry Laboratory of Bezmialem Vakıf University.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency and ratio values were used in descriptive statistics of the data. The distribution of variables was measured by Kolmogorov-Smirnov test. Mann-Whitney U test was used for the analysis of quantitative independent data. The chi-square test was used for the analysis of qualitative independent data and the Fischer test was used when the chi-square test conditions were not met. Effect level and cut-off value were investigated with receiver operating characteristic curve. SPSS 22.0 program was used for analysis. P values less than 0.05 were considered statistically significant.

RESULTS

Forty-three pregnant women, including 20 preeclamptic and 23 normotensive women, were included in the study. The demographic and gestational characteristics of the groups are shown in Table 1. The age, gravida and parity were higher in the preeclampsia group, and but there was no difference between the groups in terms of body mass index.

Regarding sFlt-1 and PGF levels, sFlt-1 levels and sFlt-1/PGF ratio were higher and serum PGF levels were lower in preeclamptic women compared to the control group (Figures 1, 2, 3). sFlt-1 was 146.4 ± 61.2 ng/mL, PGF was 122.3 ± 195.9 pg/mL and sFlt-1/PGF ratio was 2.4 ± 1.8 in the preeclampsia group, and sFlt-1 was 35.0 ± 35.8 ng/mL, PGF was 172.1 ± 194.2 pg/mL and sFlt-1/PGF ratio was found to be 0.3 ± 0.3 in the normotensive group (Table 2).

DISCUSSION

The imbalance between angiogenic factors such as VEGF and PGF and antiangiogenic factors such as sFlt-1 and s-Eng has been suggested to play a role in the pathogenesis of preeclampsia by causing endothelial dysfunction (4, 5).

Leanos-Miranda et al. (7) found that proteinuria, creatinine, urea, sFlt-1 values were high and PGF values were low in preeclamptic

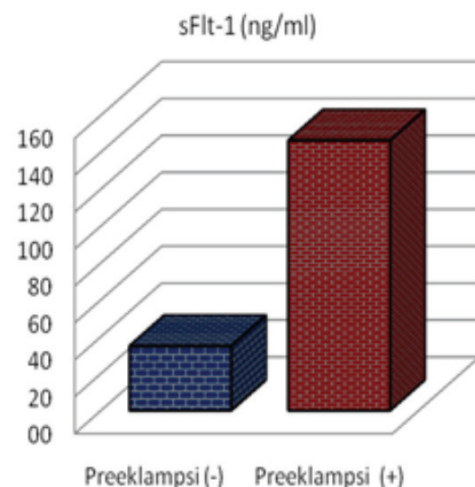


Figure 1. sFlt values (ng/mL)
sFlt: Soluble Fms-like tyrosine kinase-1

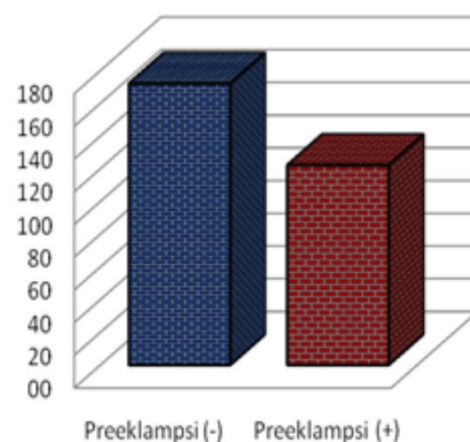


Figure 2. PGF values (pg/mL)
PGF: Placental growth factor

pregnant women. In our study, sFlt-1 levels and sFlt-1/PGF ratio were higher and serum PGF levels were lower in preeclamptic women compared to the control group.

McElrath et al. (8) found high sFlt-1 and low PGF levels in pregnant women with preeclampsia. They stated that these changes began to occur before the clinical course of the disease and were related to the severity of the disease.

Rana et al. (9) studied 616 pregnant women and found that preeclampsia developed in patients with high sFlt-1/PGF ratio and that this increase was more pronounced in pregnancies less than 34 weeks.

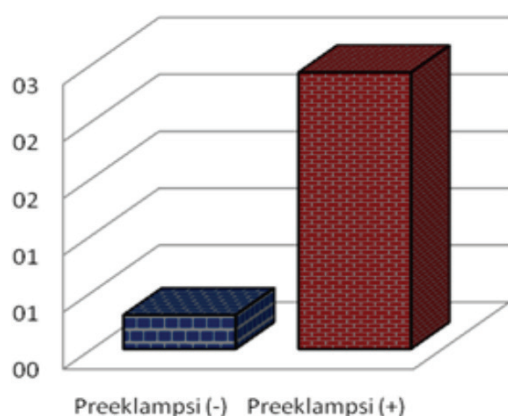


Figure 3. sFlt-1/PGF ratios
sFlt: Soluble Fms-like tyrosine kinase-1, PGF: Placental growth factor

Hunter et al. (10) only examined serum PGF level in pregnant women at risk for preeclampsia and found a negative predictive value of 98% in pregnancies less than 34 weeks and 69% in pregnancies more than 34 weeks for predicting preeclampsia in two weeks. They suggested that control of PGF levels below 34 weeks might be useful in predicting the development of preeclampsia.

Verlohren et al. (11) found the sensitivity and specificity of sFlt-1 and PGF as 90% in predicting preeclampsia in pregnancies less than 34 weeks and the sensitivity as 74% in predicting preeclampsia in pregnancies more than 34 weeks.

Baltajian et al. (12) divided 100 women with suspected preeclampsia into two groups with high and low sFlt-1/PGF ratio, and found that negative obstetric results were more common in 43 women with a high sFlt-1/PGF ratio.

Zeisler et al. (13) stated that preeclampsia did not develop at least one week in pregnant women with low sFlt-1/PGF ratio, and that there is increased risk of developing preeclampsia in pregnant women with high ratio in four weeks and recommended increasing follow-up frequency.

CONCLUSION

In conclusion, it is important to predict pregnant women at risk for preeclampsia, and early diagnosis is necessary to reduce

Table 1. Comparison of demographic and gestational features between groups

	Preeclampsia (-)		Preeclampsia (+)		p	
	Mean ± SD / n-%	Median	Mean ± SD / n-%	Median		
Age	28.3±5.7	29.0	33.4±6.5	35.0	0.011	m
BMI (kg/m ²)	31.0±4.2	30.5	30.6±5.6	30.3	0.551	m
Smoking	No	22 95.7%	19 95.0%		1.000	χ ²
	Yes	1 4.3%	1 5.0%			
Gravida	2.4±1.6	2.0	3.5±1.8	4.0	0.038	m
Parity	1.0±1.1	1.0	1.8±1.3	2.0	0.039	m
Systolic blood pressure (mm/Hg)	111.7±12.7	110.0	155.0±30.3	160.0	0.000	m
Diastolic blood pressure (mm/Hg)	72.2±10.4	70.0	97.5±20.7	100.0	0.000	m

SD: Standard deviation, BMI: Body mass index

Table 2. Comparison of sFlt-1 and PGF and sFlt/PGF ratios between groups

	Preeclampsia (-)		Preeclampsia (+)		p	
	Mean ± SD / n-%	Median	Mean ± SD / n-%	Median		
sFlt-1 (ng/mL)	35.0±35.8	21.0	146.4±61.2	136.1	0.000	m
PGF (pg/mL)	172.1±194.2	107.8	122.3±195.9	71.8	0.016	m
sFlt-1/PGF	0.3±0.3	0.2	2.4±1.8	2.2	0.000	m

sFlt: Soluble Fms-like tyrosine kinase-1, PGF: Placental growth factor, SD: Standard deviation

maternal and fetal morbidity. Although sFlt-1, PGF and sFlt/PGF ratio may be used for this purpose, large randomized controlled trials are needed for their widespread use.

Ethics

Ethics Committee Approval: This study was planned following approval from Clinical Research Ethics Committee of Okmeydanı Training and Research Hospital, University of Health Sciences (approval no: 28.06.2016/501).

Informed Consent: Written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.K., S.N.K.Ç., Concept: T.K., V.M., Design: T.K., V.M., Data Collection or Processing: T.K., S.N.K.Ç., B.B., Analysis or Interpretation: T.K., O.Ş., G.D., Literature Search: T.K., Writing: T.K., V.M.

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

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Approach to Patients with Neurotrauma and Thoracic Trauma and Anesthesia Management with Current Guidelines -1

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Abstract

There are many causes of trauma such as traffic accidents, work accidents and falling from height. These patients require systematic management in post-traumatic evaluation, airway management, resuscitation, possible surgical procedures, intensive care follow-up and treatment. The nature of the trauma, post-traumatic uncontrolled bleeding, coagulation anomalies, hypothermia, shock and acidosis disrupts the normal homeostatic mechanism and is associated with poor clinical outcome. Other paradox in trauma patients is the necessity for emergency intervention with insufficient medical history information of the patient and unclear trauma type. In this review, it was aimed to discuss the general management and anesthesia management of patients with neurotrauma and thoracic trauma in the light of current guidelines.

Keywords: Neurotrauma, thoracic trauma, anesthesia, guidelines

INTRODUCTION

In our country, approximately 7000-10000 people die after head and/or spinal trauma. The leading causes of death and permanent disability in this patient population are head trauma, hemorrhages, sepsis and multiple organ failure. Mortality rates due to severe head trauma have decreased significantly in recent years, being 20-30%. In addition to advances in computerized tomography (CT), early surgical intervention, intracranial pressure (ICP) and perfusion pressure monitoring, and progresses in intensive care unit, the increased understanding of the harmful effects of hypoxia, hypotension and hypoperfusion on the brain has undoubtedly played an important role. The algorithms applied in the early diagnosis and intervention process for the centers serving more patients play an important role in reducing the morbidity and mortality rates.

NEUROTRAUMA

A. Head Trauma

Patients with major trauma are primarily evaluated with ABC criteria, Airway, Breathing and Circulation, followed by evaluation of Glasgow Coma Scale (GCS) (Table 1). Patients with GCS ≤ 8 account for only 1% of all cases (1). Rapid imaging for advanced examination is the second stage. Patients with minor head trauma, good general condition and GCS: 15 usually do not require additional advanced imaging, while patients with GCS ≤ 14 , confusion and neurological deficit undergo advanced imaging modalities. CT is the first choice in intracranial hemorrhage and cranial fractures. The most common pathology of the skull is fractures. Most of them are linear nondisplaced fractures and discharged after 24-hour clinical follow-up. Emergent surgery is considered for patients with displaced fractures ≥ 10 mm, open wound and cerebrospinal fluid (CSF) leakage (2).



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Traumatic subarachnoid hemorrhage (SAH) is the most common hemorrhage in intracranial hemorrhages with a rate of 2.5% (Figures 1a, 1b, 1c, 1d, 1e.) (3). This is followed by hemorrhagic contusion, subdural hemorrhage (2%) and epidural hematoma (1%). Clinical manifestations of traumatic SAH range from asymptomatic patients to comatose patients. Support should be provided with clinical follow-up. Most contusions represent an abrupt acceleration and deceleration of the head, causing the brain to collide with the inner surface of the skull (coup-contre coup lesions). While most of the patients are discharged after anti-edema treatment and follow-up, some patients underwent surgical decompression due to the pressure effect and developing raised ICP.

Subdural hemorrhages occur in acute and chronic forms. Acute subdural hemorrhage occurs after tearing of the bridge veins and parenchymal damage in high-energy head traumas. There is a 60% mortality risk. While small subdural hemorrhages are managed conservatively, subdural hemorrhages that are ≥ 1 cm or that create ventricular shift undergo emergency surgery. Chronic subdural hematoma usually presents with a more insidious symptomatology. Elderly patients, infants or patients with coagulopathies usually present with unilateral motor deficits and headache following head trauma. They may be unilateral or bilateral and require urgent neurosurgical intervention. Surgical technique is based on the drainage of the hematoma by unilateral/bilateral burr holes or craniectomy. Epidural hemorrhage develops after rupture of the epidural

arteries (especially middle meningeal artery) following skull fracture after head trauma. Although the patient's general status at the time of admission is fine, the patient may suddenly worsen and become comatose. This phenomenon is known as the lucid interval. Epidural hemorrhages ≤ 10 mm can be followed, while larger diameter hematomas are decompressed surgically. The intracranial localization of the hematoma (such as temporal or posterior fossa localization), as well as the hematoma volume, is indicative in the surgery of epidural hematomas.

The supportive treatment of hospitalized patients with severe head trauma, confusion and intracranial hemorrhage starts with head position. In order not to disturb the cerebral blood circulation, the head is held at 30 degrees in neutral position, the patient's oral intake is discontinued and isotonic fluid support is given. The hemoglobin value should not be below 10 g/dL in order not to impair cerebral perfusion. Blood pressure should be kept between 120/80-160/90 mmHg. The risk of intracerebral hemorrhage increases with hypertension and the risk of cerebral hypoperfusion increases with hypotension. If cerebral edema is detected in the patient, mannitol or hypertonic saline is administered at a dose of 0.25-1 g/kg within 20 minutes. Because of cytotoxic edema, there is no use of glucocorticoids such as dexamethasone after head trauma. Since intubated patients with a GCS of ≤ 8 cannot be followed up, ICP monitoring should be performed. "Cerebral perfusion pressure: mean arterial pressure -ICP" formula is the main and indispensable formula of patient follow-up. While ICP changes with age in normal individuals, the

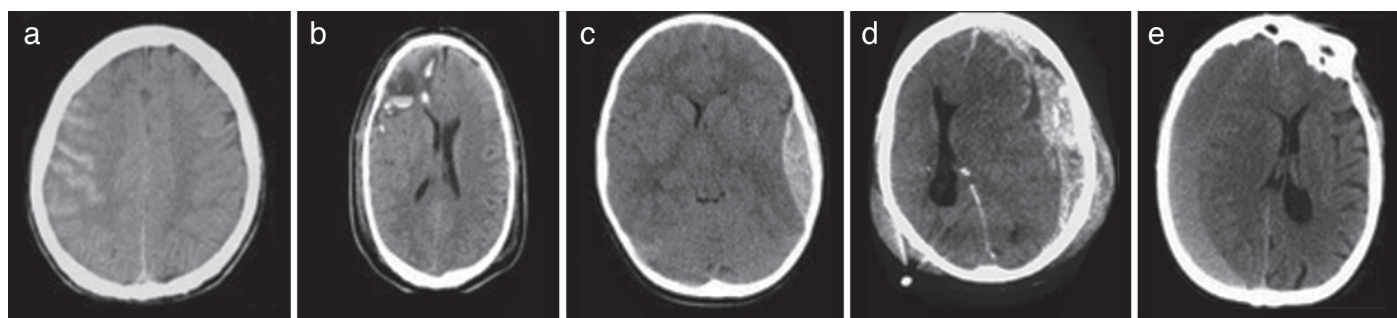


Figure 1. a) Traumatic subarachnoid hemorrhage, b) contusion, c) epidural hematoma, d) subdural hematoma (acute) and e) subdural hematoma (chronic)

Table 1. Glasgow Coma Scale		
Eye response	Verbal response	Motor response
Spontaneously (+4)	Oriented (+5)	Obeys commands (+6)
To verbal command (+3)	Confused (+4)	Localizes pain (+5)
To pain (+2)	Inappropriate words (+3)	Withdrawal from pain (+4)
No eye opening (+1)	Incomprehensible sounds (+2)	Decorticate response (+3)
	No verbal response (+1)	Decerebrate posture (+2)
		No motor response (+1)

normal value in adults is 8-12 mmHg, 3-7 mmHg in pediatric population and 1.5-6 mmHg in newborns (4). If ICP cannot be lowered despite all anti-edema treatments, ventricular drainage, barbiturate coma, and, finally, decompressive craniectomy can be used in patients with an ICP >20 cm H₂O (5, 6). Morbidity and mortality rates are extremely high in these patients. Patients with post-traumatic hydrocephalus are followed with external ventricular drainage (4).

The use of prophylactic antiepileptic drugs is always controversial despite intracranial hemorrhage due to head trauma. While some centers begin prophylactic antiepileptics, antiepileptic medication is recommended in recent publications if the patient experiences two seizures more than 24 hours apart (7). Diphenylhydantoin was the first option in the past with a bolus dose of 15-20 mg/kg in 150 cc saline (not to exceed 50 mg/kg per minute) and a maintenance dose of 3x100 mg, levetiracetam 2x500 mg is widely used nowadays due to being non-hepatotoxic and having less side effects.

B. Spinal Trauma

According to ultrasonography data, the incidence of posttraumatic spinal cord injury was reported to be 40/1000000 and 12,000 annually (8). Traffic accidents are the leading cause. This is followed by falls from the height and assaults (9). Patients are admitted to our emergency department on a trauma board by an ambulance and cervical collar is applied by emergency

personnel. After the ABC evaluation and general examination of the patient, neurological examination is performed. The impairment scale developed by American Spinal Injury Association (ASIA) is used by our neurosurgeons to assess the degree of trauma (Table 2). Patients often describe pain in the midline at thoracic and lumbar spinal levels. Spinal neurological damage should be suspected in the presence of sensory or motor deficits in the extremities or urinary and stool incontinence.

In our practice, the first imaging modality to be asked is CT because of its sensitivity in bone tissue. Depending on the location of the examination, local CT or whole spinal CT may be requested. Spinal column is evaluated in 3 separate sections as anterior, middle and posterior columns. Fractures on the anterior colon, and transverse process and spinous process fractures are usually followed only by analgesic treatment and braces, while the fractures in the vertebral bodies are indications for hospitalization. The compression rate and spinal cord compression should be examined carefully. The cases with less than 50% compression are managed conservatively with thoracolumbar brace at outpatient follow-up, while surgery is planned in patients with >50% loss of height (Figures 2a and 2b) or 30% or more spinal canal involvement and free bony fragment in the canal (Figures 3a and 3b). According to the general condition of the patient, surgery is planned for decompression and stabilization within the first 24-48 hours. The presence of

Table 2. ASIA spinal trauma assessment scheme

Patient Name _____
 Examiner Name _____ Date/Time of Exam _____

ASIA STANDARD NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY **ISCOS**

MOTOR
 KEY MUSCLES (scoring on reverse side)

R	L	
<input type="checkbox"/>	<input type="checkbox"/>	Elbow flexors
<input type="checkbox"/>	<input type="checkbox"/>	Wrist extensors
<input type="checkbox"/>	<input type="checkbox"/>	Elbow extensors
<input type="checkbox"/>	<input type="checkbox"/>	Finger flexors (distal phalanx of middle finger)
<input type="checkbox"/>	<input type="checkbox"/>	Finger abductors (distal finger)

UPPER LIMB TOTAL (MAXIMUM) + =
 (25) (25) (50)

Comments: _____

L2	<input type="checkbox"/>	Hip flexors
L3	<input type="checkbox"/>	Knee extensors
L4	<input type="checkbox"/>	Ankle dorsiflexors
L5	<input type="checkbox"/>	Long toe extensors
S1	<input type="checkbox"/>	Ankle plantar flexors

Voluntary anal contraction (Yes/No)

LOWER LIMB TOTAL (MAXIMUM) + =
 (25) (25) (50)

SENSORY
 KEY SENSORY POINTS

0 = absent
 I = impaired
 N = normal
 NT = not testable

Any anal sensation (Yes/No)

PIN PRICK SCORE (max: 112)
 LIGHT TOUCH SCORE (max: 112)

TOTALS (MAXIMUM) (50) (50) (100) (100)

NEUROLOGICAL LEVEL: The most caudal segment with normal function

SENSORY	R	L
MOTOR	<input type="checkbox"/>	<input type="checkbox"/>

COMPLETE OR INCOMPLETE? Incomplete - Any sensory or motor function in S4-S5
 ASIA IMPAIRMENT SCALE

ZONE OF PARTIAL PRESERVATION: Caudal extent of partially innervated segments

SENSORY	R	L
MOTOR	<input type="checkbox"/>	<input type="checkbox"/>

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simultaneous thoracic trauma is the main reason for postponing the surgical intervention. If a motor-sensory deficit due to spinal trauma is considered, high-dose methylprednisolone protocol is started. If the trauma occurs within 8 hours, 30 mg/kg methylprednisolone is delivered with bolus infusion for 15 minutes. Then, 5 mg/kg is started as maintenance dose in 24 hours. The patient should have gastrointestinal hemorrhage prophylaxis and blood glucose monitoring. The maintenance dose is extended up to 48 hours if the hospital admission is after 8 hours. Although the exact benefits of the methylprednisolone protocol have still not been confirmed, there are publications in the literature showing that there is significant recovery in motor and sensory deficits in the first 8 hours, despite the possibility of an additional high complication rate (10).

In conclusion, a significant part of the experimental and clinical trials in the last 20 years have focused on cell biochemistry and genetics to further understand the pathophysiology of head trauma, and it is thought that the developments in this area will contribute greatly to directing clinical treatment in the future. As being the members İstanbul Okmeydanı Training and Research Hospital, one of İstanbul's and Turkey's most patient serving center, approaching the head and spinal traumas based

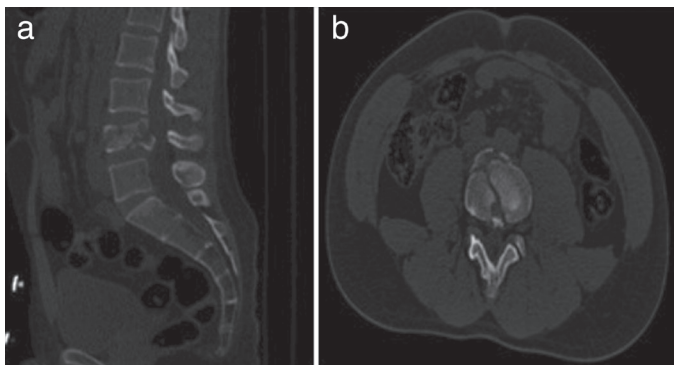


Figure 2. a,b) L4 vertebrae compression fracture in sagittal and axial computerized tomography sections. Free fragment is observed in the spinal canal

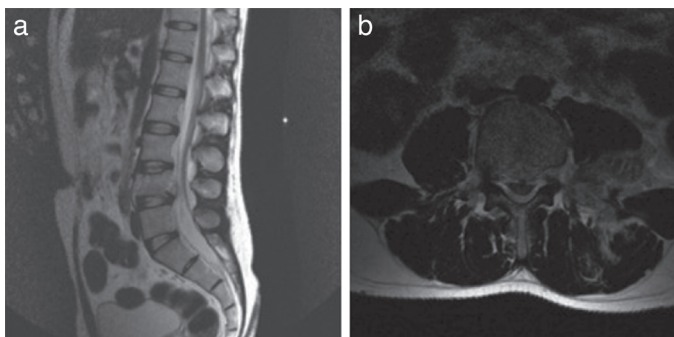


Figure 3. a,b) Sagittal and axial magnetic resonance imaging sections of the same patient

on current guidelines will provide a faster and more systematic evaluation of the patient, and will help us reach the desired numbers in morbidity and mortality rates.

THORACIC TRAUMA

Thoracic traumas are an important cause of mortality and morbidity in adults and children. It is the leading cause of death in patients with multiple traumas with a rate of 25%, but this rate decreases to 1% in isolated thoracic penetrating injuries not accompanied by cardiac injury. The first aim of the approach to thoracic trauma is to eliminate the situations that may result in death in a short time. According to etiology, thoracic trauma is divided into blunt and penetrating trauma. Specific injuries include pulmonary barotrauma, burns of the tracheobronchial tree resulted from aspiration, blast lung injury, parenchymal lung damage from aspiration and iatrogenic injuries. Rib fractures with blunt trauma may involve lung contusions, lacerations, or rupture. In addition to such direct damages, it may also be secondary to disintegration of the tissue (air embolism resulting from the entrance of air into the pulmonary veins after lung laceration) (11).

The most common cause of blunt trauma is traffic accidents (70%). Penetrating thoracic traumas occur as a consequence of side arms or firearms and are classified into three groups (12, 13):

1. "Sleeper" wounds (no exit wound)
2. Perforating wounds (entrance wound and exit wound)
3. Wounds in which the projectile penetrates through the whole intra-thoracic cavity and remains in the subcutaneous tissue.

It should be always borne in mind that all penetrating traumas are in direct communication between the external environment and the pleural space. If the defect is large, an open pneumothorax occurs. In small defects, wounds close spontaneously due to the contraction of muscle or blood clotting. However, this may cause tension pneumothorax and empyema, making the patient more complicated (14-16).

Pathophysiology of Thoracic Trauma

Traumatic force with thoracic trauma impairs lung function by causing:

-Disorder in the mechanics of breathing: caused by rib fractures and flail chest. Accompanied with hypoventilation, atelectasis, difficult expectoration of sputum from the tracheobronchial tree, the development of bronchopneumonic complications, acute respiratory failure and even death, especially with elderly

patients. Collapse of the lungs due to hemo- or pneumothorax leads to arteriovenous shunt and hypoxia (11-14).

-Disruption in ventilation-perfusion relationship: oxygenation cannot be performed with the lung collapse or mechanical obstruction of the large airway. Systemic hypoxia occurs. This lung damage may cause vascular thrombosis or massive fat microembolism, disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS) (10-16).

-Gas exchange abnormalities of alveolocapillary membrane: the alveolocapillary membrane is composed of the surfactant layer, the surface of macrophages, alveolar epithelium, the interstitial space and the capillary endothelium. In thoracic trauma, direct damage to the alveolocapillary membrane may occur, as in the case of lung contusion, smoke inhalation, aspiration of gastric contents, heart failure and pulmonary interstitial edema (12-16).

Surgical Approach to Thoracic Trauma

The main task of the surgeon is to determine the mortality risk of the wound and determine the type of the intervention. Conditions requiring hospitalization include (11-17):

- Airway obstruction
- Massive hemothorax
- Tension pneumothorax
- Open pneumothorax
- Flail chest
- Cardiac tamponade
- Massive bilateral lung contusion
- Elderly patient with multiple fractures

Thoracotomy or thoracoscopy are indicated in the cases of (18-20):

- Open pneumothorax
- Penetrating injuries due to foreign bodies
- Bleeding complications of chest drain
- Massive hemothysis
- Continuous air leak from the chest drain and permanent collapse of the lung
- Tracheobronchial injury
- Cardiac tamponade
- Damage to large blood vessels and heart

-Diaphragm and esophagus injuries

-Empyema due to complication of the injury

The surgeon must first decide rapidly by physical examination. Radiological imaging and laboratory tests are time-consuming in severe cases. Clinical judgment is needed to decide upon the necessity for tracheostomy, chest drainage, emergency pericardiocentesis or thoracotomy. Anamnesis also includes an important place in emergency patient evaluation. For example, patients who were run over in road traffic accidents or those crushed in motor vehicle accidents are expected to have severe intra-thoracic injuries. Deceleration injuries indicate potential injuries to aorta and large airway. In patients admitted with symptoms of hypotension, distended neck veins may point to possible cardiac compression, tension pneumothorax or cardiac tamponade. On the other hand, collapsed neck veins are mainly associated with hypovolemic shock. Examining the chest wall may indicate paradoxical breathing due to flail chest and palpation may reveal fractures or subcutaneous emphysema. Isolated chest trauma resulting from blunt trauma is very rare. The most common extra-thoracic injuries in polytraumatized patients are cranial injuries, abdominal injuries, extremity fractures, pelvic fractures and vertebral fractures (13, 21, 22). Entrance and/or exit wounds should be observed, but such wounds should not be probed in penetrating thoracic injuries. If the entrance penetrating injury is below the fifth rib, it is necessary to investigate the possibility of diaphragmatic rupture and intra-abdominal organ injury. Abdominal injury should be evaluated in patients with rib fractures below the 7th rib. Exploration of the abdomen in patients with blunt chest and abdominal injuries is recommended first. Thoracic exploration is performed if the patient's condition is still unstable after abdominal bleeding is controlled.

If there is no need for emergency thoracotomy or if developing tension pneumothorax is excluded, the patient is directed to radiological procedures. Radiographically overlooked or undiagnosed conditions are soft tissue injury, bone fractures, diaphragm injuries, mediastinal expansion, foreign body and pneumomediastinum. For example, up to 35% of the patients with a ruptured diaphragm appear to have normal chest X-ray (23, 24).

The first thing that should be done after the first interventions in thoracic trauma is the patient's analgesia and initiation of respiratory physiotherapy (25-28).

Diagnostic Procedures with Thoracic Trauma

Each blunt trauma patient should first undergo anteroposterior and lateral chest radiography (29). If there is a penetrating

trauma, the entrance and exit wounds must be marked with radiosensitive markers. A surgeon carefully and systematically interprets chest radiographs in order not to overlook some possible injuries. The surgeon must check (30-32):

- The correct placement of the endotracheal tube
- Pneumothorax
- Tension pneumothorax
- Hemothorax
- Mediastinal emphysema: presence of air in the neck is the most specific finding and the most common cause is pneumothorax.
- Lung contusion: it cannot be seen on initial radiographs, but increased opacity should raise suspicion for further investigations.
- The protrusion of intra-abdominal organs into the thorax: on the left side the finding of hydroaeric collection may be mistaken for hydropneumothorax. Radiographic diagnosis of diaphragmatic rupture on the right side is difficult, as the liver is most commonly herniated organ. Elevation of the right hemidiaphragm should raise suspicion for further investigations.
- Fractures
- Projectiles in the thorax
- Mediastinal expansion: it is a major finding indicating aortic rupture. It is significant when it is larger than 8 cm.

When the patient's condition is relatively stable, it is recommended to use chest CT in additional diagnostic procedure. Ultrasound is a useful method for evaluation of the subdiaphragmatic space findings and when small collections of fluid in the pleural space are detected, and also for cardiac evaluation.

Monitoring of Thoracic Trauma

The recommended parameters to monitor in thoracic trauma are arterial pressure, heart rate (obtained by electrocardiogram), central venous pressure, cardiac index, arterial PO₂, PCO₂ and pH, and hematocrit value (33-37). Initial hematocrit values may be unreliable, especially in patients with excessive blood loss who receive crystalloid solutions. Hematocrit value can be accepted as a useful tool for determining the type of fluid rather than the fluid volume replacement. During replacement, it is important to stabilize the systolic pressure at 90-mmHg in order to correct hypovolemia and to prevent hypervolemia.

Shock in Thoracic Trauma

In the early stages of shock, venous flow to the heart (preload) is reduced due to the loss of circulating fluid, which causes

decreased cardiac output and the development of hypotension and tissue hypoperfusion. The body strives to maintain a normal circulating volume by moving fluid from tissues into blood vessels, by increasing heart rate due to activation of the sympathetic nervous system and by reduction of diuresis due to vasoconstriction. In later stages of shock, at the cellular level hypoxia is compensated by anaerobic metabolism and lactic acid production, leading to the development of metabolic acidosis. If the shock is left untreated, edema occurs and the cells lose functions. For this reason, correct fluid replacement therapy should be initiated immediately (35). The average blood loss per fractured rib is approximately 150 mL, and in hemothorax it can be 2 L.

Acute Respiratory Distress Syndrome

It is a life-threatening condition and is characterized by non-cardiogenic pulmonary edema, hypoxemia, decreased lung compliance, intrapulmonary shunt and progressive pulmonary fibrosis in the late stage (36).

- Acute lung injury
- ARDS

In the first group, there is mild hypoxemia. In the second group, there is severe hypoxemia. Common features include acuteness, bilateral infiltrates and pulmonary artery occlusion. Predisposing risk factors for the first group are pulmonary contusion, aspiration of gastric contents, pneumonia, inhalation injury and drowning, and severe traumatic shock, head trauma, abdominal sepsis, burns, fat embolism, excessive volume replacement and DIC for the second group (38, 39). Clinical manifestations include tachypnea and tachycardia during the first 12 hours. The patients use auxiliary respiratory muscles, and on auscultation they have high-pitched expiratory crackles. Progressive hypoxia, hypercapnia, and acidosis are observed. Chest X-ray shows diffuse spotty infiltrations. The treatment of ARDS requires mechanical ventilation. The primary aim is to keep the alveoli open. Therefore, positive end-expiratory pressure (PEEP) is kept high. Fluid should be reduced in order to prevent pulmonary edema. The intravascular volume should be maintained at the lowest level. Vasopressors and inotropes can be used, and nitric oxide inhalation can be performed (40, 41). The effect of steroids on ARDS is only in preventing fibrosing alveolitis.

Blunt Chest Injuries

Chest wall contusion and hematoma are the most common thoracic injuries. Being mostly extrapleural, these injuries do not require surgery (18). Rib fractures occur in about 35% of thoracic injuries. Mortality is approximately 10% in elderly people over

65 years. Rib fractures in children are rare, since the chest wall in children is very flexible, and the mortality rate is about 5%. A severe traumatic force is required for fracture of first, second and third ribs posteriorly and first and second ribs anteriorly (19). Injuries of large blood vessels or tracheobronchial tree should be kept in mind in these fractures. Flail chest is a medical condition when three adjacent ribs are double-broken unilaterally. The frequency of flail chest is about 5%. There is paradoxical respiration. The injured segment of the chest wall is drawn inward during inspiration and is drawn outward during expiration. The treatment of flail chest can be conservative or operative. Conservative treatment is recommended in patients with posterior type of flail chest without dyspnea. The application of mechanical ventilation with PEEP should be tried as a last chance for patients who will undergo surgery. If no result is obtained, surgery is required (21).

Sternal fractures result from blunt trauma with high-energy. They are often associated with multiple rib fractures. Sternal fracture is typically transverse and localized to the upper and middle parts of body of sternum. If the broken fragments were pushed over to the mediastinum, surgery would be indicated.

Lung contusion represents parenchymal laceration accompanied by intra-alveolar hemorrhage. Chest CT is the gold standard. A contusion involving more than 30% of lung parenchyma requires mechanical ventilation. Emergency surgery is needed in only 5%. The indications include contusions with a massive air leak and injuries with massive intra- thoracic hemorrhage (1500 mL of blood on insertion of the thoracic drain or 200 mL of blood every 4 hours, with continuous replacement).

Traumatic injuries of the trachea and bronchi present with hemoptysis, localized pain, neck contusion, subcutaneous emphysema, inspiratory stridor, hoarseness, progressive dyspnea and Hamman's sign (auscultatory findings of "crackling" synchronized with the heartbeat and breathing) in the early period, and dyspnea, stridor and distal infections in the late period. They are not often diagnosed immediately. Fiberoptic bronchoscopy is the gold standard in suspected cases (31).

Foreign bodies in the tracheobronchial tree is often seen in the injured with lost consciousness, in patients with dysphagia and in small children. Posteroanterior chest radiography should be performed first. Diagnosis and treatment are combined in patients with suspected radiological findings and anamnesis. It is treated by rigid bronchoscopy. In case of chronic foreign bodies, with developed granular tissue around the foreign body, bleeding or perforation can be seen in this area, but it is rare. Treatment of this complication is 100% surgery.

Traumatic injuries of diaphragm occur in 4% of all blunt traumas. This rate is 15% in stab wounds and 45% in gunshot wounds. Diagnosis is made based on the radiographic findings. Undiagnosed patients may present with strong pain within the chest, dyspnea and signs of obstruction in small and large intestine. Treatment is surgical. Diaphragmatic injuries diagnosed in the early period are treated by laparotomy and injuries diagnosed in the late period are treated by thoracotomy. Because it is more difficult to reach the diaphragm by thoracotomy, and thoracotomy is preferred because of the adhesions in the chest in late cases (34).

Traumatic pneumothorax is the presence of air in the pleural space and occurs as a consequence of the laceration of the visceral pleura and lung parenchyma. The laceration of parietal pleura can contribute to the development of subcutaneous emphysema. There is no necessity of associated rib fracture in blunt traumas. During sudden chest compression, alveolus rupture may be seen due to increased alveolar pressure. Air that comes out in the interstitial area by dissection toward the visceral pleura or mediastinum results in pneumothorax or mediastinal emphysema. In addition, pneumothorax may occur due to lung injury or air entering from outside as a result of penetrating injuries. Pneumothorax is surgically treated by the thoracic drainage. If there is no previous lung disease, decreased vital capacity is well tolerated by the patient. However, in case of previous lung diseases, a progressive course from respiratory insufficiency and alveolar hypoventilation to metabolic acidosis may occur. There are 3 types pneumothorax, namely simple, open and tension type. Open pneumothorax is often associated with penetrating injury, while the remaining two are mainly seen at the blunt injury of the chest.

Pneumothorax occurs due to the injury of the following structures (39):

- Thoracic wall
- Lung parenchyma
- Tracheobronchial tree out of the part covered by the mediastinal pleura
- Esophagus and mediastinal pleura
- Diaphragm and associated perforations of intestines

PA chest X-rays in the standing position is the gold standard in the diagnosis. In the management of tension pneumothorax, a large cannulated injector or angiocath should be inserted to drain the air if the patient is going to be transferred or if a drain

is to be inserted. Minimal pneumothorax or patients presenting late to hospital with minimal pneumothorax may be treated conservatively, but this is rare.

Subcutaneous emphysema defines the presence of the air within the subcutaneous tissue. It should not be confused with gas due to abscess formation within the tissue. The mediastinal emphysema will gradually intensify in the head and neck region of the patient due to the upward movement of the air. This is not clinically relevant unless it causes dyspnea (32). The areas that disturb the patient may be carefully drained with a subcutaneous needle.

Traumatic hemothorax marks the presence of blood within the pleural space. Besides blunt and penetrating traumas, it can also be seen as iatrogenic. After surgery of thoracic spine, especially vertebrae at the level Th4-Th6, hemothorax can develop even a few days after the surgery. Empyema may develop over hemothorax. The decision of hemothorax is not given by the color of the fluid; the hematocrit value of the pleural fluid should be at least 50% of the blood hematocrit value. Incidence of hemothorax in blunt trauma is 38% in patients with rib fracture and 35% without rib fracture. The occurrence of hemothorax is more frequent when the fractured rib-ends are dislocated. The treatment of massive hemothorax is surgery. The non-massive hemothorax cases are followed by thoracic drainage. The tomography is the gold standard in the diagnosis (39-42).

Absolute Indications for Thoracic Drainage

- Traumatic pneumothorax
- Tension pneumothorax
- Bilateral pneumothorax
- Massive hemothorax
- Associated collection of blood and air - hemopneumothorax

Indications for Re-Drainage

- Development of empyema at the drained hemothorax
- Encapsulated hydroaeric collections
- Collections of fluid and air

In patients with general anesthesia requirement for surgeries of extra-thoracic organs, PEEP levels and ventilation pressures should be kept low, and attention should be paid to the possibility of development of the tension pneumothorax. Preventive drainage of the thorax is not indicated when the obvious signs of pneumothorax are not present.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: N.T., T.M., A.A., M.E., Design: N.T., T.M., A.A., M.E., Data Collection or Processing: T.M., A.A., C.K., M.E., Analysis or Interpretation: N.T., T.M., A.A., M.E., Literature Search: T.M., S.T., A.A., M.E., Writing: T.M., C.K., S.T., A.A., M.E., İ.A.

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Bilateral Central Retinal Vein Occlusion Secondary to Essential Hypertension

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Abstract

A 44-year-old male patient presented to the emergency department with bilateral vision loss and bilateral retinal central vein occlusion was detected. The patient was consulted to internal medicine and cardiology departments to investigate the etiology. Blood pressure, sedimentation rate, blood glucose, lipid profile, plasma protein electrophoresis, blood biochemistry, thyroid function tests, homocysteine, Protein C and S resistance, factor V Leiden mutation, rheumatoid factor, anti-nuclear antibody, serum angiotensin converting enzyme, syphilis antibodies, electrocardiogram, carotid Doppler ultrasonography and urinary system ultrasonography were investigated. Primary hypertension was detected in the patient and other results were negative. Etiology should be extensively investigated, especially in patients with bilateral retinal vein occlusion and patients with retinal vein occlusion under the age of 50.

Keywords: CRVO, bilateral retinal vein occlusion, etiology

INTRODUCTION

Central retinal vein occlusion (CRVO) is a cause of visual loss that can be seen at any age (1, 2). While 90% of patients with CRVO are older than 50 years, only 10% are under 40 years of age (1, 3). The central retinal vein is particularly susceptible to obstruction in the lamina cribrosa region, where the retinal vein and central retinal artery pass close to each other. Arteriosclerosis of the adjacent central retinal artery can cause central retinal vein compression, which prevents blood flow. Decreased blood flow results in increased pressure and may lead to thrombosis, which can lead to vascular occlusion (2). Systemic risk factors for CRVO include hypertension, diabetes mellitus, ischemic heart disease, bleeding disorders, vasculitis and autoimmune diseases (4). CRVO may be bilateral especially in patients under 40 years of age. Hypercoagulability, hyperviscosity syndromes and inflammatory conditions should be considered in these patients (5-7).

CASE REPORT

A 44-year-old male patient was admitted to the emergency department with loss of vision in both eyes. In the history of the patient, it was learned that vision loss in the right eye occurred one week before and he lost vision in the left eye today. In the examination of the patient, visual acuity in the right eye was "hand motion" and 2/10 in the left eye. Fundus examination revealed bilateral CRVO. The patient was referred to the retina clinic. The diagnosis was confirmed with fundus fluorescein angiography. Simultaneous systemic research was performed with the internal medicine and cardiology departments because of the patient being young and having bilateral CRVO. The examinations are shown in Table 1. As a result of the examinations, the patient was diagnosed with essential hypertension. In order to prevent further complications, anti-hypertensive treatment was started.



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Table 1. Examinations performed in the patient and their results

Examination	Result
Arterial blood pressure	160/90 mmHg
Sedimentation rate	Normal
Blood glucose level	Normal
Blood biochemistry	Normal
Lipid profile	Normal
Plasma protein electrophoresis	Normal
Thyroid function tests	Normal
Homocysteine levels	Normal
Protein C and S resistance	Negative
Factor V Leiden mutation	Negative
RF and ANA levels	Negative
Serum ACE level	Normal
Syphilis antibodies	Negative
ECG	Normal
Carotid Doppler US	Normal
Urinary US	Normal
RF: Rheumatoid factor, ANA: Anti-nuclear antibody, ACE: Angiotensin converting enzyme, ECG: Electrocardiography, US: Ultrasound	

DISCUSSION

Central retinal arteries and veins pass through a narrow opening in the lamina cribrosa and pass through a common adventitious sheath. The limited area here causes a tendency for circulatory and venous insufficiency in the eyeball. In cases such as hypertension and arteriosclerosis, the arterial wall becomes stiffer and compresses the veins. This pressure results in a tendency to thrombosis in the vein wall. In this patient, we believe that bilateral CRVO was due to hypertension-induced venous compression.

In the literature, hyperviscosity-induced bilateral CRVO were reported (1, 2). Similar to our patient, a case of bilateral CRVO due to malignant hypertension has been reported in the literature (8). Although the patient reported in the study of Zsuzsa B. et al., (8) had malignant hypertension, our patient had essential hypertension.

Hypertension is a disease that should be considered since there are no symptoms or warning signs. Patients may experience ischemic heart disease, stroke, or renal failure, as well as loss of vision as in our case. Cardiologists, nephrologists, internal

medicine physicians and ophthalmologists should consider general and atypical causes when evaluating CRVO in order to prevent further ophthalmic and systemic complications. Detailed systemic examination should be performed especially in patients with bilateral CRVO and in young patients.

Ethics

Informed Consent: Writing consent of the patient was received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.H.B., A.Ç., Concept: A.H.B., A.Ç., S.B., Design: B.E., Data Collection or Processing: A.H.B., B.E., Analysis or Interpretation: A.H.B., A.Ç., B.E., Literature Search: S.B., Writing: A.H.B., M.E.

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The Use of Integrated Pulmonary Index in Cardiopulmonary Resuscitation

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Keywords: Cardiopulmonary resuscitation, integrated pulmonary index, return of spontaneous circulation

Dear Editor,

Recent studies have shown that various biomedical devices are used for return of spontaneous circulation (ROSC). End-tidal carbon dioxide (ETCO₂) measurement in cardiopulmonary resuscitation (CPR) is also included in the guidelines as the gold standard for ROSC (1). Kalkan et al., (2) measured the blood flow in abdominal organs and the brain using near infrared spectrophotometry in CPR and demonstrated the importance of increasing values in showing ROSC. One of these devices, Capnostream 20p (Capnostream® 20, Oridion, Jerusalem, Israel) measures respiratory rate, pulse rate, saturation and ETCO₂, and gives a mathematical value [integrated pulmonary index (IPI)] for assessing the patient's ventilation level and associated tissue perfusion. This device provides numerical values between 1 and 10. Values less than 7 indicate worsening of breathing and tissue perfusion, and advanced airway requirements (3). Studies have also reported that patients with an IPI score less than 4 require advanced airway support (4). Our study was planned on the basis that ETCO₂ is used to calculate IPI values and is capable of predicting spontaneous circulation. Our aim was to investigate initial IPI values in cases of out-of-hospital cardiac arrest, together with the IPI trend during CPR and its association with absence of presence of ROSC. We planned to enroll 50 patients with or without ROSC. Our aim was to measure IPI values in patients with non-hospital cardiac arrest and to analyze whether these were

predictive of ROSC. Our basic hypothesis is that IPI values at time of admission are low. We anticipated that these would increase after proper CPR, and that as IPI values increased, tissue perfusion would be established and spontaneous circulation would be restored. Spontaneous circulation was not restored in six of the first eight patients. IPI values during admission and throughout CPR were measured as 1 (however, ETCO₂ values were increasing, showing that these patients had no intubation problems). ROSC was achieved in the remaining two patients, but IPI values were still 1. No increase was observed in measured values in any of our patients. However, under normal conditions, appropriate CPR establishes both respiration and circulation. Measurements may be expected to increase in the absence of any pulmonary pathology. We therefore suspected the possibility of an error in our methodology, and we have reviewed the details of the IPI. By using Ambu-bag, we ventilate the patient 8-10 times per minute and ensure the respiratory rate among the four parameters considered in IPI. We also provide heart rate with active heart massage and saturation by giving oxygen with advanced airway. The ETCO₂ level is obtained with variable values in the trend graph. IPI values being a constant 1, although different levels might be expected with different practitioners, derives from the fact that the IPI shows the presence of a vital critical level, at the same algorithmic level, in the loss of one of these four functions in the patient. We do not think IPI will also be



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able to predict spontaneous circulation in CPR, although this device is highly suitable for showing respiratory status and for deciding intubation. However, further studies with larger patient populations may support our hypothesis.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.Ü., Concept: A.K., Design: A.K., Data Collection or Processing: S.Ü., Analysis or Interpretation: S.Ü., Literature Search: S.Ü., Writing: S.Ü.

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