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İÇİNDEKİLER/CONTENTS
Araştırma Makaleleri /Research Articles

İÇİNDEKİLER/CONTENTS
Araştırma Makaleleri /Research Articles

Osmangazi Tıp Dergisi
Osmangazi Journal of Medicine 2021; 43(3):197-201

Research Article / Araştırma Makalesi

The Prognostic Value of Fascin 1 and Galectin 3 in Laryngeal Carcinoma

Larenks Kanserinde Fascin-1 ve Galectin-3'ü n Prognostik Önemi

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Abstract

The aim of this study was to evaluate the prognostic relevance of fascin-1 and galectin-3 that are actin proteins in laryngeal cancer. Informatios and documents of 58 patients diagnosed with advanced laryngeal squamous cell carcinoma and treated surgically were included in the study. Surgical specimen slides were stained immunohistochemically at Benchmark staining platform by Ventana Universal DAB detection kit. For each marker, least 1000 cells were counted at light microscope. For galectin-3; more than 5% staining was considered as positive, %5 and less was accepted as negative. For fascin-1; staining intensity was categorized in 4 groups; 0: no staining; 1: weak staining; 2: moderate staining; 3: strong staining,and the percentage of positive cells was grouped from 1 to 4 as follows; 1: ≤ 10 %; 2:10-50 %; 3: 50-75 %; 4: ≥75. Then, two scores gathered and final score 4 and less accepted as low staining; 5 and more accepted as high staining. Fascin-1 expression was found high in 41(70.68 %); and galectin-3 expression was found positive in 36 (62.06 %) patients. Fascin-1 and galectin-3 expressions showed no correlation with conventional prognostic factors, disease free survival and disease related death, statistically. Prognostic value of fascin-1 and galectin-3 in laryngeal cancer could not be demonstrated in this study. However, this study may contribute to the literature in this respect, as these two markers have not been studied together in any study of laryngeal cancer until now. Therefore, more studies are needed on this subject.

Keywords: fascin-1, galectin-3, actin protein, prognosis, laryngeal cancer

Özet

Bu çalışmada birer aktin proteini olan fascin-1 ve galektin-3'ün larenks kanserinin prognozu ile ilişkilerinin değerlendirilmesi amaçlanmıştır. İleri evre laringeal skuamöz hücreli karsinom tanısı alan ve cerrahi olarak tedavi edilen 58 hastaya ait bilgi ve belgeler retrospektif olarak incelendi ve çalışmaya dahil edildi. Cerrahi spesmene ait patoloji preperatları Ventana Universal DAB tespit kiti ile Benchmark boyama platformunda immünohistokimyasal olarak boyandı. Her bir işaretleyici için ışık mikroskobunda en az 1000 hücre sayıldı. Galektin-3 için; % 5'in üzerinde boyanma pozitif,% 5 ve altı boyanma negatif olarak kabul edildi. Fascin-1 için; boyanma yoğunluğu 4 grupta kategorize edildi; 0: boyannma yok; 1: zayıf boyama; 2: orta derecede boyanma; 3: güçlü boyanma ve pozitif hücrelerin yüzdesi 1 ile 4 arasında gruplandı; 1: ≤% 10; 2:% 10-50; 3:% 50-75; 4: ≥75. Ardından elde edilen iki puan toplandı ve 4 ve daha düşük nihai puan düşük boyanma olarak; 5 ve üzeri yüksek boyanma olarak kabul edildi. Fascin-1 ekspresyonu 41 (% 70.68) hastada yüksek bulundu; galektin-3 ekspresyonu 36 (% 62.06) hastada pozitif bulundu. Fascin-1 ve galektin-3, geleneksel prognostik faktörler, hastalıksız hayatta kalma ve hastalıkla ilişkili ölüm ile istatsitiksel olarak hiçbir korelasyon göstermedi. Larenks kanserinde fascin-1 ve galektin-3'ün prognostik değeri bu çalışmada gösterilememiştir. Ancak bugüne kadar herhangi bir larenks kanseri çalışmasında bu iki belirteç birlikte çalışılmadığı için bu çalışma literatüre bu açıdan katkı sağlayabilir. Bu nedenle bu konuda daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: fasin-1; galektin-3;aktin proein;prognoz; larenks kanseri

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1. Introduction

Early diagnosis increases the chance of survival in laryngeal cancer. However, especially in developing countries, the number of patients diagnosed at advanced stage is still rather high. Worldwide reported 5-year overall survival rate for patients with advanced laryngeal cancer is around 50 – 60 %, and despite all technological advances in diagnostic and treatment methods of oncology, satisfactory improvement at long-term survival rates couldn't be achieved in these patients. According to general oncologic view, the survival rate depends on characteristics of tumor, patient and type of applied treatment.1-3 Still today, the most frequently and practically used prognostic factors are stage of the tumor and pathological characteristics such as size, grade of tumor, perineural and lymphovascular invasion, and nodal status.4,5 However, it is possible to encounter patients with different course of disease having similar tumor characteristics. Therefore, a lot of study is carried out on new prognostic factors. Especially, studies on molecular biomarkers are more remarkable. Fascin-1 and galectin-3 are also examples for these molecular biomarkers.6-8

Fascin-1 and galectin-3 are proteins that are barely or never present in healthy epithelial tissues in human, but their expressions have been shown in various malignant epithelial tumors of body, and it is believed they have an important role in cancer progression and metastasis. Fascin-1 is an actin binding protein that is responsible for forming of bundles like lamellipodia and invadopodia make main skleton of cellular protrusion of cancer cells to enhance cellular motility7,8. Galectin-3 is a carbohydrate binding protein that is thought to play role in tumor growth, cell growth, apoptosis inhibition, and cell adhesions.6,9-11

Many studies have shown prognostic relevance of fascin-1 in gastric, colorectal, breast, lung, and laryngeal carcinoma. However, the prognostic value of galectin-3 in epithelial malignancies has been studied only in a few studies, and the results are conflicting. To the best of our knowledge, prognostic value of these 2 biomarkers have never been investigated together in laryngeal carcinoma. We aimed to address this subject in this study.

2. Methods

Study Design & Participants

This study was carried out retrospectively. The study protocol was approved by the local ethics committee with the number 2011/05 and was supported with the number 201111035 by Project Development and Support Unit of our university.

The hospital files of patients diagnosed with advanced laryngeal squamous cell carcinoma and treated surgically between January 2003 and February 2011 were retrieved. After exclusion criteria (having a history of chemotherapy and/or radiotherapy before surgery, a following time shorter than one year, and a positive primary tumor margin) were met, 58 patients were included in the study.

Cigarette smoking was evaluated by using Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking).

Immunohistochemical Study

All of surgical specimen slides of these 58 patients were stained immunohistochemically at Benchmark staining platform (Ventana Medical Systems Inc) by Ventana Universal DAB detection kit. As primary antibodies, Fascin-1 (clone FCN01, Neomarkers, Fremont, CA, USA; dilution 1:100) and Galectin-3 (clone 9C4, Leica Biosystems, Novocastra, Newcastle Upon Tyne, UK; dilution 1:100) were used. After staining, sections were dehydrated and closed. For each marker, least 1000 cells were counted at light microscope. For Galectin-3; more than 5% staining was considered as positive, %5 and less was accepted as negative. For fascin-1; staining intensity was categorized in 4 groups; 0: no staining; 1: weak staining; 2: moderate staining; 3: strong staining. The

percentage of positive cells was grouped from 1 to 4 as follows; 1: ≤ 10 %; 2:10-50 %; 3: 50-75 %; 4: ≥75. Two scores gathered and final score 4 and less accepted as low staining; 5 and more accepted as high staining.

Statistical analysis

SPSS15 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Kaplan-Meier method used to form survival curves and log-rank test was used for analyzing survival curves. Disease free survival (DFS) was calculated from the date of curative surgery to that clinical or pathological recurrence. Disease related death (DRD) was calculated from the date of curative surgery to that death. Chi-square test was performed for the analysis of categorical variables. Univariate survival analyses and also multivariate survival analyses, with Cox proportional hazards models, were performed separately for DFS and DRD. Significance level was set as $p < 0.05$.

3. Results

A total of 58 patients were male with a mean age of 60.4. All patients underwent total laryngectomy and neck dissection. Thirty-nine patients received adjuvant radiotherapy. Median follow-up period was 46.6 months. Median time to recurrence was 17.1 (2-35) months, disease related death was 34.4 (4-91) months. Primary tumor size varies between 0.7-7 cm (median 3.3 cm). Metastatic lymph nodes (at least 1, maximum 22) were found in 24 patients. Recurrence occurred in a total of 11 patients, 10 of whom died of disease. Table-1 presents clinic and pathologic characteristics of patients, results for fascin-1 and galectin-3 expressions, and prognostic implication of all these findings obtained by taking results of local recurrence and deaths related to disease. The correlation of fascin-1& galectin-3 expression with pathologic characteristics is shown in Table-2. Fascin-1 expression was found high in 41(70.68 %) patients and galectin-3 expression was found positive in 36 (62.06 %) patients. Positive and negative staining for galectin-3 and high and low staining for fascin-1 is shown in Figure 1 and 2. Fascin-1 and galectin-3 expressions showed no correlation with conventional clinic and pathologic prognostic factors, disease free survival and disease related death, statistically. Significant correlations were observed between 2 conventional pathologic prognostic factors (metastatic lymph node status, extracapsular extension at metastatic lymph node) and disease related death. Metastatic lymph node status, extracapsular extension at metastatic lymph node, and vascular invasion were significantly correlated with recurrence. There was no correlation between fascin-1 and galectin 3 expression.

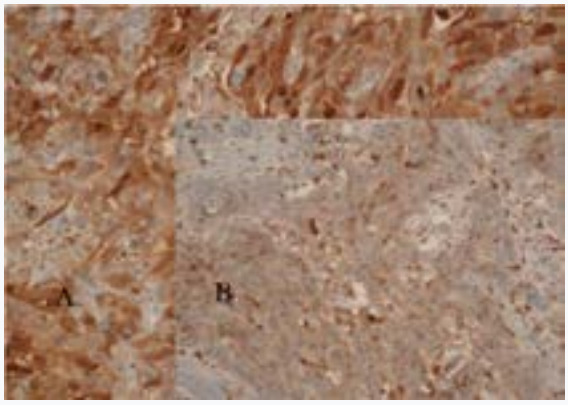

Figure 1. A.Galectin-3 high expression (x200), B. Galectin-3 low expression (x200)

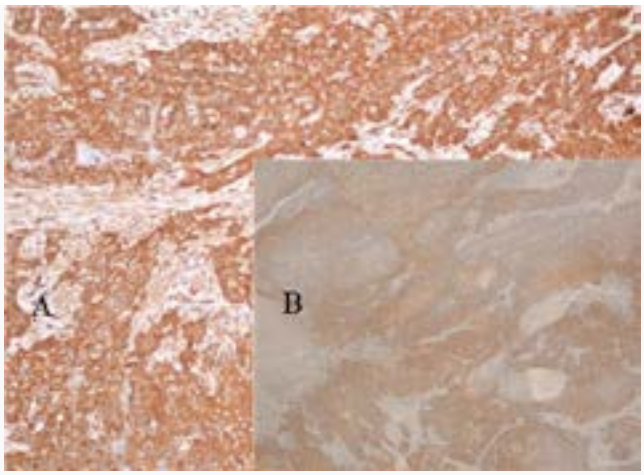

Figure 2. A.Fascin- 1 high expression (x200), B. Fascin-1 low expression (x200)

4. Discussion

This study was conducted to explore prognostic value of fascin-1 and galectin-3 in patients with advanced laryngeal carcinoma. To interpret the results accurately and comparatively, conventional clinic and pathologic prognostic factors seen in Table 1 were evaluated additionally. As a result, fascin-1 and galectin-3 expressions showed no correlation with conventional prognostic factors, disease free survival and disease related death, statistically. Nevertheless, significant correlations were observed between 2 conventional pathologic prognostic factors (metastatic lymph node status, extracapsular invasion at metastatic lymph node) and disease related death. Besides, metastatic lymph node status, extracapsular extension at metastatic lymph node, and vascular invasion were significantly correlated with recurrence. The last 2 results were not surprising, because the idea indicates lymph node metastases is the main prognostic factor for patients with laryngeal cancer is nowadays already approved by literature.

Some results related to fascin-1 and galectin-3 expression in head and neck cancers reported in literature are summarized in Table 3. As seen in this table, the overall results mentioned for fascin-1 expression is that it is inversely correlated with survival in head and neck cancer.6,9,11-18 However, the belief about galectin-3 expression is not clear in literature. Several different results have been reported about this marker. Miranda et al.16 reported insignificant relation between galectin-3 expression and disease free survival in laryngeal carcinoma, similar to us. The main reason for our statistically non-significant results of fascin-1 can be related to the insufficient number of patients, because it was remarkable that the p value ($p = 0.076$/ Table 2) indicating the relationship between fascin-1 expression and metastatic lymph node was close to significant value statistically. Table 4 shows the comparison of our study and some of the studies we benchmarked in Table 3. As seen, all of these studies have quite high patient number compared to us. This is because these studies were made in country (China) has approximately 20% of the world's population and increased cancer incidence and mortality. Besides, our study only includes advanced cancer patients most of whom treated with adjuvant radiotherapy after surgery which resulted in a low recurrence rate and high survival rate. For this reason, statistically significant correlation may not be obtained between fascin-1 and disease free survival in our study. When we compared our study with other studies in this respect, we saw that most of studies in the literature including with low number patients did not give any information about adjuvant treatment and included both early and advanced stage patients. All these comments we have made up to now may also apply to galectin-3. Even so, to speak with evidence, of course we need more large series. Nonetheless, we think this study is

valuable, because fascin-1 and galectin-3 have not been evaluated together with any previous studies in laryngeal cancer.

5. Conclusion

Although this presented study did not reveal the prognostic value of fascin1 and galectin-3 in laryngeal cancer, there are some different results in literature. To get rid of this topic, there is a need for multi-centered studies with large series.

❖ *This article was presented in 35 th Turkish National Ear Nose Throat and Head & Neck Surgery Congress, 2-6 November 2013, Antalya/Turkey*

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Research Article / Araştırma Makalesi

Vitamin D Level in Pediatric Patients with Severe Iron Deficiency Anemia

Ağır Demir Eksikliği olan Çocuk Hastalarda Vitamin D Düzeyi

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Abstract

This study aimedto determine the frequency of Vitamin D deficiency in children with severe iron deficiency anemia. This study included 60 patients with severe iron deficiency anemia between 6 and 72 months and 60 healthy children with similar age and sex. Patients diagnosed with severe iron deficiency anemia with blood hemoglobin level below 7 g/dl were included in the patient group. Regarding the etiology of anemia, a blood sample was taken from the patient group for hemogram, reticulocyte count, biochemical analyses, serum iron and iron binding capacity, transferrin saturation, ferritin, vitamin B12, folic acid and serum Vit D levels. Vitamin D deficiency (<20 ng/mL) was present in 75% (n=45) of the patient group, while 1.7% (n=1) of the control group ($p<0.001$). Vitamin D level of the patient group (16.2±13.3 ng/ml) was significantly lower than the control group (36.3±15.1 ng/ml) ($p<0.05$). While there were no children with retardation in the control group, 16.7% of the patient group had developmental retardation ($p<0.001$). Vitamin D deficiency has very high prevalence and Vitamin D level was found to be significantly low in patients with severe iron deficiency anemia. Consequently, patients with severe iron deficiency anemia should be evaluated and treated for Vitamin D deficiency.

Keywords: Severe iron deficiency anemia; Vitamin D deficiency; Childhood; Developmental retardation; Transfusion

Özet

Bu çalışmada ağır demir eksikliği anemisi olan çocuklarda Vitamin D eksikliği sıklığının belirlenmesi amaçlanmıştır. Bu çalışmaya 6-72 ay arasında ağır demir eksikliği anemisi olan 60 hasta ile benzer yaş ve cinsiyette 60 sağlıklı çocuk dahil edildi. Hasta grubuna kan hemoglobin düzeyi 7 g/dl'nin altında ağır demir eksikliği anemisi tanısı alan hastalar dahil edildi. Aneminin etiyolojisi ile ilgili olarak hasta grubundan hemogram, retikülosit sayımı, biyokimyasal analizler, serum demir ve demir bağlama kapasitesi, transferrin satürasyonu, ferritin, vitamin B12, folik asit ve serum Vitamin D düzeyleri için kan örneği alındı. Vitamin D eksikliği (<20 ng/mL) hasta grubunun %75'inde (n=45), kontrol grubunun %1.7'sinde (n=1) mevcuttu ($p<0.001$). Hasta grubunun Vitamin D düzeyi (16.2±13.3 ng/ml), kontrol grubuna (36.3±15.1 ng/ml) göre anlamlı olarak düşüktü ($p<0.05$). Kontrol grubunda gelişme geriliği olan çocuk bulunmazken, hasta grubunun %16.7'sinde gelişme geriliği vardı ($p<0.001$). Vitamin D eksikliği çok yüksek prevalansa sahiptir ve ağır demir eksikliği anemisi olan hastalarda Vitamin D düzeyi anlamlı olarak düşük bulunmuştur. Sonuç olarak, ciddi demir eksikliği anemisi olan hastalar Vitamin D eksikliği açısından değerlendirilmeli ve tedavi edilmelidir.

Anahtar Kelimeler: Ağır demir eksikliği anemisi; D vitamini eksikliği; Çocukluk; Gelişimsel gerilik; Transfüzyon

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1. Introduction

It has been difficult to identify diseases caused by nutritional deficiencies together with the improvement of living standards and the widespread use of enriched food (1,2). However, some micronutrients may be insufficient and this causes various problems (1,2). Although iron and vitamin D levels are important in the normal growth and development of children, they are often ignored (2).

Iron deficiency is the most common nutritional deficiency in children, and the prevalence of anemia worldwide is found to be 32.9% in 2010, and it has been reported that children under 5 are most commonly affected (3). There are studies reporting that the prevalence in our country is around 7-9% (4). Vitamin D is a fat-soluble vitamin. foods naturally contain vitamin D, vitamin D dermal synthesis is the main source. (5). Vitamin D sourced from diet or the Although very few dermal synthesis is not biologically active and enzymatic reactions are required to turn it into active metabolites (5). Serum 25-OH-D levels which indicate deposits of Vitamin D in the body are generally low in cases such as rickets and osteomalacia. (5). Although the incidence of nutritional rickets varies according to age and regions, the most common age is between 3-18 months (6). It is known that vitamin D deficiency and iron deficiency anemia are related (7). A number of studies shows that vitamin D has an effective role in erythropoiesis (8). Besides vitamin D has erythropoietic functions, it also has effects on iron metabolism and immune system (9). It is thought that vitamin D regulates systemic cytokine production and therefore reduces the inflammatory process in chronic disease /inflammation anemia (9).

Vitamin D deficiency, which can be seen with severe iron deficiency anemia, can cause growth retardation and important problems in children. This study has been planned to determine the frequency of vitamin D deficiency in children with severe iron deficiency anemia.

2. Materials and Methods

Our study included 60 patients with severe iron deficiency anemia between 6-72 months and 60 healthy children of the same age group. Ethics committee approval (2018/02-09; 17.01.2018) was obtained from Clinical Research Ethics Committee and then the study was started prospectively. The parents of the children included in the study were given detailed information about the study and a written informed consent was obtained.

Severe iron deficiency, as in the definition of World Health Organisation (WHO); blood hemoglobin level was considered to be below 7 g/dl (10). Patients diagnosed as severe iron deficiency anemia with blood hemoglobin level below 7 g/dl were included in the patient group. While establishing the control group, the criteria of being compatible with the patient group in terms of age and gender, and not having any chronic disease or anemia were taken as a basis.

Of all cases age, sex, body weight in kilograms, height in centimeters, head circumference in centimeters, breast milk intake status, and whether they received erythrocyte suspension was recorded. Taking into account the body measurement rates, children are classified according to whether they have growth and developmental delays. Evaluation of cases in terms of developmental retardation was made according to the definition that growth rate was not suitable for the age and according to the age, body weight, and head circumference percentiles were evaluated (11). Those with developmental retardation were selected from those whose height and body weights were below 3 percentile according to the age.

For the etiology of anemia from the patient group, hemogram, reticulocyte (N:0.76-2.25%), serum iron (N:50-175 mg/dl), iron binding capacity (N:250-450 µg/dl), transferrin saturation (N:>15%), ferritin (N:10-250 µg/L), vitamin B12 (N:211-911 pg/ml), folic acid (N:5.38-24 ng/ml), and for vitamin D (N:20-70 ng/ml) serum level tests a blood sample was taken. From the control

group a blood sample was taken for the serum Vitamin D levels, hemogram, ferritin, folic acid and vitamin B12 tests. The results obtained were compared statistically. In this study, serum vitamin D level lower than 20 ng/ml was defined as vitamin D deficiency.

Ferritin, vitamin B12 and folic acid tests were studied using commercially available kits in Cobas 8000 c 702 system autoanayzer (Roche Diagnostics, Rotkreuz, Switzerland), Hemogram and reticulocyte count in Symex XN-3000 autoanalyzer (Sysmex Corporation, Kobe, JAPAN). Vitamin D level was studied with Dionexultimate 3000 uHPLC analyzer (Thermofisher scientific, US).

Statistical Analysis

The results obtained from the experiments were evaluated by using the statistical package program "SPSS 18.0 for Windows". The conformity of the data to normal distribution was tested with the Kolmogorov-Smirnov and Shapiro Wilk Tests. "Independent Sample T Test" was used in the analysis of independent samples that fit the normal distribution and whose variances are homogeneous, and "Mann-Whitney U Test" was used in the analysis of data that did not fit the normal distribution and whose variances were not homogeneous. “Chi-square Test” was used in the analysis of qualitative data. Pearson correlation coefficients were used to analyze the relationship between parameters that provide parametric test conditions, and Spearman correlation coefficients to analyze the relationship between parameters that do not meet parametric test conditions. All values are shown as mean (standard deviation) and/or median (minimum-maximum). The probability of error (p value) was set to 0.05 for statistical significance.

3. Results

Our study included 60 patients with severe iron deficiency anemia between 6-72 months and 60 healthy children of the same age group. The mean age of the patient group was 20.52±16.36 months, while the control group was 20.60±16.33 months (p=0.939). In the patient and control groups, boys were 60% and girls 40% (p=1.000) (Table 1). The average number of siblings of children in the patient group was 2.17±1.82 (median=2, min-max=0-10).The frequency of vitamin D deficiency (<20 ng/ml) was significantly higher in the patient group 75% (n=45) when compared to the control group 1.7% (n=1) (p<0.001). Breastfeeding rate was 95% (n=57) in the patient group. Erythrocyte suspension transfusion was given to 53.3% of the patient group. When the histories of breastfeeding were questioned, only 5.0% of them never took breast milk. Finally, 63.3% of patients with severe anemia use vitamin D preparations. When the body weight, height, head circumference measurements and growth retardation were compared between the patient and control groups, the mean body weight was 10.7±2.7 kg in the patient group and 11.4±3.6 kg in the control group; mean height was 78.9±10.5 in the patient group, 82.4±12.9 cm in the control group, and the mean head circumference was 45.4±2.3 in the patient group, and 46.2±1.8 cm in the control group. There was no significant difference between the patient and control groups in terms of these three variables (p>0.05). While none of the subjects in the control group had developmental retardation, 16.7% (n= 10) of the patient group had developmental retardation. In the patients, developmental retardation was found more frequently than the controls (p<0.001) (Table 2). In the patient group; WBC (White Blood Cell) was 9960±3172 mm3, RBC (Red Blood Cell) was 4.4±0.6 x106/mm3, HGB (Hemoglobin) was 6.1±0.8 g/dl, HCT (Hematocrit) was 23.8±2.8, MCV (Mean Corpuscular Volume) was 54.3±4.2 fL, MCH (Mean Corpuscular Hemoglobin) was 13.9±1.8 pg, MCHC (Mean Corpuscular Hemoglobin Concentration) was 25.6±1.7 g/dl, RDW (Red Cell Distribution Width) was 22.7%, MPV (Mean Corpuscular Volume) was 8.9±0.5 fL, PLT (Platelet Count) was 528±233 x103/mm3, folic acid was 12.8±6.1 ng/ml, ferritin was 7.7±9.2 µg/L, vitamin B12 was 431.8±311.6 pg/ml and vitamin D was 16.2±13.3 ng/ml (Table 3). When the patient and control groups were compared; RBC, HGB, HCT, MCV, MCH, MCHC, MPV, ferritin, folic acid and vitamin D (Figure 1) levels were significantly higher in the control group when compared to the patient group (p<0.05) (Table 3). In contrast,

RDW, monocyte and PLT levels were significantly higher in the patient group when compared to the control group ($p<0.05$) (Table 3). There was no significant difference between the patient and control groups in terms of WBC, neutrophils, lymphocytes, eosinophils and vitamin B12 ($p>0.05$) (Table 3). In addition, iron binding capacity in the patient group was 442.64±81.89 µg/dl (median=454.00 µg/dl, min-max=281.00-603.00 µg/dl), transferrin saturation was 3.94% (median=2.93%, min-max=0.70-15.00%) and reticulocyte was 1.92% (median=1.73%, min-max=0.05-5.20%).

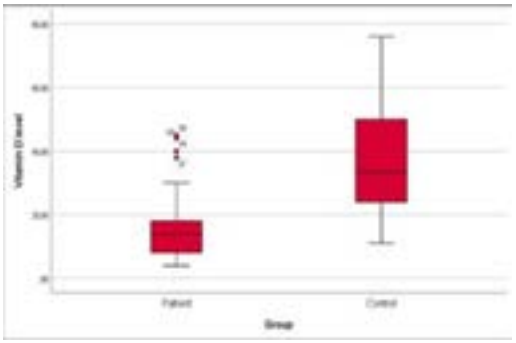

Figure 1. Vitamin D levels in patient and control groups.

Table 1. Comparison of age and gender in the patient and control groups

	Group				Total		p
	Patient		**Control**				
	N	%	N	%	n	%	
Gender							
Female	24	40.0	24	40.0	48	40.0	1.000**
Male	36	60.0	36	60.0	72	60.0	
Age (Month)							
Mean (SD)	20.52±16.36		20.60±16.33		20.56±16.27		0.939*
Median (min-max)	14.50 (6-72)		15.00 (6-72)		15.00 (6-72)		

*SD = standard deviation, * Mann Whitney U test, ** Chi-square Test*

Table 2. Comparison between patient and control groups in terms of body weight, height and head circumference measurements.

Group	Patient	Control	p
Body weight (kg)			
Mean±SD	10.7±2.7	11.4±3.6	0.205*
Median (min-max)	10.5 (5.8-18.0)	10.5 (7.2-27.0)	
Height (cm)			
Mean±SD	78.9±10.5	82.4±12.9	0.098*
Median (min-max)	77.5 (58.0-108.0)	80.5 (63.0-123.0)	
Head circumference (cm)			
Mean±SD	45.4±2.3	46.2±1.8	0.100*
Median (min-max)	45.5 (39.0-49.0)	46.0 (42.0-50.0)	

*SD = standard deviation, * Mann Whitney U test, ** chi-square test*

Table 3. Comparison of laboratory test results in patient and control groups

Group	Patient			Control			p
	Mean±SD	Median	Min- Max	Mean±SD	Median	Min- Max	
WBC (mm^3)	9960±3172	9325	3940-19940	9506±2546	9375	5160-16380	0.430**
RBC ($x10^6/mm^3$)	4.4±0.6	4.5	3.1-5.6	4.8±0.4	4.8	4.0-5.9	**<0.001****
HGB (g/dL)	6.1±0.8	6.4	3.7-7	12.1±0.8	12.0	11.0-14.1	**<0.001***
HCT (%)	23.8±2.8	24.6	16.4-27.9	36.2±2.3	36.0	32.3-42.6	**<0.001***
MCV (fL)	54.3±4.2	54.5	45.1-71.4	75.8±4.0	76.0	70.0-83.8	**<0.001***
MCH (pg)	13.9±1.8	13.8	11.1-22.8	25.1±2.1	25.3	18.7-28.5	**<0.001***
MCHC (g/dL)	25.6±1.7	25.4	21.4-31.9	33.2±1.3	33.2	29.5-35.9	**<0.001****
RDW (%)	22.7±2.8	22.2	18.4-31.1	14.5±2	14.1	12.3-23	**<0.001***
MPV (fL)	8.9±0.5	8.9	8-10	9.4±0.6	9.3	8.2-11.2	**<0.001****
Monocyte (mm^3)	934±473	840	340-2630	742±204	700	470-1370	**0.025***
PLT ($x10^3/mm^3$)	528±233	498.5	150-1341	368±88	354.5	214-598	**<0.001***
Folic acid (ng/ml)	12.8±6.1	12	2-31.6	18.8±7	17.8	9-40	**<0.001***
Ferritin (µg/L)	7.7±9.2	4.1	0.5-48.6	29.3±22.1	23	4-106.5	**<0.001***
Vit B12 (pg/ml)	431.8±311.6	357	145-1582	436.4±213.2	381.5	145-1073	0.157*
Vit D (ng/ml)	16.2±13.3	14	3.4-71	36.3±15.1	31.5	11-76	**<0.001***

*WBC: White Blood Cell, RBC: Red Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Cell Distribution Width, PLT: Platelet count, MPV: Mean Platelet Volume, SD = standard deviation, * Mann Whitney U test, ** Independent t test*

Correlation coefficients and statistical evaluations showing the relationship between parameters in the patient group are given in Table 4. There was a statistically significant negative correlation between age, body weight and height and WBC, lymphocyte and folic acid, and a statistically significant positive correlation between vitamin B12 levels. There was a statistically significant positive correlation between head circumference and RBC and HCT values. There was a statistically significant positive correlation between folic acid and MCH and lymphocyte values. There was a statistically significant negative correlation between vitamin B12 and lymphocyte, PLT and folic acid levels. There

was a statistically significant positive and folic acid levels ($p<0.05$) (Table 4). correlation between vitamin D and eosinophil

Table4. Correlation coefficients and statistical evaluations showing the relationship between parameters in the patient group

		Age (Month)	Body weight (kg)	Height (cm)	Head circumference (cm)	Folic acid (ng/ml)	Vit B12 (pg/ml)	Vit D (ng/ml)
Age (Month)	r	-	0.824	0.842	0.573	-0.433	0.389	-0.157
	p	-	**0.001**	**0.001**	**<0.001**	**0.001**	**0.002**	0.230
Body weight (kg)	r	0.824	-	0.835	0.601	-0.367	0.362	-0.186
	p	**<0.001**	-	**0.001**	**<0.001**	**0.004**	**0.005**	0.155
Height (cm)	r	0.842	0.835	-	0.546	-0.331	0.462	-0.119
	p	**<0.001**	**0.001**	-	**<0.001**	**0.010**	**0.001**	0.365
Head circumference (cm)	r	0.573	0.601	0.546	-	-0.206	0.091	-0.111
	p	**<0.001**	**0.001**	**0.001**	-	0.143	0.520	0.433
WBC (mm^3)	r	-0.281	-0.338	-0.370	-0.122	0.030	-0.147	0.078
	p	**0.030**	**0.008**	**0.004**	0.388	0.818	0.263	0.553
RBC ($x10^6/mm^3$)	r	-0.133	0.024	0.011	0.295	0.013	0.008	-0.167
	p	0.309	0.857	0.932	**0.034**	0.922	0.949	0.203
HGB (g/dL)	r	-0.157	-0.099	-0.159	0.189	0.214	-0.087	-0.035
	p	0.231	0.452	0.224	0.179	0.100	0.509	0.792
HCT (%)	r	-0.066	0.047	-0.038	0.299	0.105	-0.128	-0.178
	p	0.615	0.723	0.770	**0.032**	0.424	0.331	0.174
Lymphocyte (mm^3)	r	-0.525	-0.533	-0.474	-0.126	0.340	-0.327	0.203
	p	**<0.001**	**0.001**	**0.001**	0.375	**0.008**	**0.011**	0.120
PLT ($x10^3/(mm^3)$)	r	-0.141	-0.137	-0.280	0.044	0.009	-0.352	0.100
	p	0.282	0.297	**0.030**	0.758	0.943	**0.006**	0.447
Reticulocytes (%)	r	-0.148	-0.088	-0.227	-0.003	-0.010	-0.366	-0.118
	p	0.259	0.501	0.082	0.983	0.938	**0.004**	0.371
Folic acid (ng/ml)	r	-0.433	-0.367	-0.331	-0.206	-	-0.371	0.321
	p	**0.001**	**0.004**	**0.010**	0.143	-	**0.004**	**0.012**
Vit B12 (pg/ml)	r	0.389	0.362	0.462	0.091	-0.371	-	-0.060
	p	**0.002**	**0.005**	**0.001**	0.520	**0.004**	-	0.646

Vit D (ng/ml)							
	r	-0.157	-0.186	-0.119	-0.111	0.321	-0.060	-
	p	0.230	0.155	0.365	0.433	**0.012**	0.646	-

WBC: White Blood Cell, RBC: Red Blood Cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, RDW: Red Cell Distribution Width, PLT: Platelet count, MPV: Mean Platelet Volume, Spearman correlation coefficients (r = correlation coefficient, p = level of significance)

4. Discussion

Together with the improvement of living conditions, it is difficult to determine the diseases caused by nutritional deficiencies as a result of widespread use of enriched foodstuffs. However, some micronutrients are inadequate and cause various problems. Iron and vitamin D are two important micronutrients in children's normal growth and development. In this study, we found that patients with severe iron deficiency anemia had significant vitamin D deficiency.

The vitamin D content of breast milk is low, and the American Academy of Pediatrics recommends 400 IU vitamin D supplements per day to babies who are breastfed, regardless of whether they receive formulation support or not(12). In our study, the rate of breastfeeding was 95% (n = 57) in the patient group. The data we obtained are similar to these studies, and those with severe iron deficiency anemia often switch late to supplementary food during feeding and are fed only with breast milk, and vitamin D deficiency is common in these patients.

Iron deficiency anemia is one of the causes of growth and development retardation as well as many clinical problems (13). Soliman et al. (13) evaluated 40 children with iron deficiency anemia in terms of growth and development before and after treatment and reported that iron deficiency anemia impairs growth and development. In our study, there was no developmental retardation in any cases of the control group, while 16.7% (n=10) of the patient group was determined developmental retardation. The parameters reflecting the state of anemia; hemoglobin levels, hematocrit, MCV, RBC and MPV were found to be low in the patient group consistent with the literature. Mean ferritin levels were also lower in the patient group when compared to the control group, consistent with the literature. Also, reactive thrombocytosis was seen in iron deficiency anemia (14). As consistent with the literature in also our study, the mean platelet count of the patient group was higher than that of the control group.

In our study, the frequency of vitamin D deficiency (<20ng/ml) was significantly higher in the patient group 75% (n=45) compared to the control group 1.7% (n=1). We found that the mean vitamin D level was significantly lower in the patient group (16.2±13.3 ng/ml) when compared to the control group (36.3±15.1 ng/ml).

Vitamin D has been shown to play a role in erythropoiesis and vitamin D deficiency poses a great risk for anemia (8). In addition, vitamin D deficiency can decrease erythropoietin receptor expression from stem cells and cause anemia (16). Iron is an essential element for cytochrome P450 functions and some of these cytochromes (CYP27A1, CYP24A1) play a role in vitamin D hydroxylation (17). Iron deficiency can affect the functions of these enzymes and lead to vitamin D deficiency (17). Our study confirms the literature information. Since patients with anemia have chronic fatigue and weakness, their exposure to the sun decreases, and as a result, sufficient sunlight exposure cannot be provided for vitamin D synthesis (15). Kartal et al. (18) reported that they have reservations about the association of iron deficiency anemia and vitamin D deficiency, that measurement methods, nutrition, medications and infections may affect this association, and that more comprehensive studies should be conducted considering these factors. Smith et al. (19) stated that vitamin D supports erythropoiesis and creates a protection against anemia.In our study, vitamin D levels were found to be significantly low in patients with severe iron deficiency.

Jin et al. (20) in their study, which included 102 children in 2010-2011; found 67% vitamin D deficiency in children with iron deficiency anemia. In the same study, it was found that vitamin D levels were below normal in those with iron deficiency anemia and there was a significant relationship between hemoglobin and 25 (OH) D levels (20). In addition, although iron supplementation did not improve the vitamin D level in patients, a positive correlation was found between the serum iron level of the patients and vitamin D levels (21). Kaymak Cihan et al. (7) found that iron deficiency anemia and vitamin D deficiency were related to each other in their study, which included 117 children Sharma et al. (22) reported that anemia was observed statistically significantly in children with vitamin D deficiency in their study involving 263 children.

In our study, when the serum vitamin D levels of the patient and control groups were compared; the mean vitamin D level of the patient group was found to be statistically significantly lower than that of the control group. However, in the correlation analysis, no correlation was found between the vitamin D levels of the patient group and the laboratory parameters for anemia. In the light of these data, we concluded that iron deficiency anemia and vitamin D deficiency are related entities, similar to the literature reviews mentioned above.

There are some limitations of our study. One of them is; patients with moderate and mild iron deficiency anemia or only iron deficiency who did not develop anemia yet were not included in the study. More studies are needed on iron deficiency and vitamin D relation in these patient populations. Other limitations of our article include the fact that the time of breastfeeding and the time of starting supplementary food were not specified. In addition, the lack of data on post-treatment blood values and development of the patients can be considered as another limitation. Studies including this point are needed with more cases. The strength of our study is it is the first study to investigate Vitamin D levels in patients with severe iron deficiency anemia.

5. Conclusion

In conclusion, the frequency of vitamin D deficiency was found to be high and vitamin D level was significantly low in patient with severe iron deficiency anemia. Therefore, it was concluded that vitamin D levels should be routinely evaluated in patient with severe iron deficiency anemia and support should be provided accordingly.

Contributors'Statement:

MC,CA,HG,FT,NSA,FIT,: conceptualized the research design and protocol, provided inputs on the research tool, analysis and interpretation of the data, and contribute to manuscript writing and revised it;

MC,CA,HG,FT,NSA,FIT: administrative and technical guidance on the research, design of research, and provided critical inputs on writing of the manuscript;

MC,CA,HG,FT,NSA,FIT: contributed to research design, conceptualized the research tool, and inputs to manuscript writing;

MC,CA,HG,FT,NSA,FIT: data collection, analysis, manuscript writing;

MC,CA,HG,FT,NSA,FIT analyzed the study results, supported interpretation and contributed to the manuscript writing and revision. All authors approved the final version of manuscript, and are willing to be accountable for all aspects of study.

Abbreviations:*Vitamin D; WBC, white blood cell RBC; red blood cell, HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; PLT, platelet count; MPV, mean platelet volume.*

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Research Article / Araştırma Makalesi

First Treatment in Burns: Evaluation of Treatment Attempts at Scene

Yanıkta İlk Tedavi: Olay Yerindeki Tedavi Uygulamalarının Değerlendirilmesi

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Abstract

To determine and evaluate the first treatments applied just after injury at scene or at primary/secondary care health institutions to burn patients before admission to a burn center and to provide suggestions to increase awareness in first treatment of burns. Between November 1, 2019 and December 31, 2019 300 burn patients, who admitted for the first time to the outpatient clinics of our tertiary burn center and agreed to participate were included in this descriptive-cross-sectional study. Patient data and the first treatments applied at the scene or another health care institution were evaluated. There were 153 male (51.0%) and 147 female (49.0%) patients. Scalds with tea (n=96) and water (n=79) was the most common etiology for burns. The percentage of burned total body surface area was 3.82±4.8. The first intervention was performed at the scene in 79% (n=237) patients, while in a health institution in 21% (n=63). 73.8% (n=175) of interventions at scene and 39.7% (n=25) of 63 interventions performed in a health institution were not appropriate. Patients or their parents who admitted to our outpatient burn clinic did not have enough information about first aid in burns. With education programs for mothers, awareness can be raised about indoors childhood burns and appropriate first intervention. For protection and correct intervention in workplaces, education on occupational health and safety should be continued seriously. There were also deficiencies in treatments performed in health institutions. In this regard in-service training to health personnel would be beneficial.

Keywords: Burns; first treatment; awareness;

Özet

Çalışmanın amacı, yaralanmadan hemen sonra olay yerinde veya birinci/ikinci basamak sağlık kuruluşunda yanık merkezine gönderilmeden önce yanan hastalara uygulanan ilk tedavileri belirleme ve değerlendirmenin yanı sıra yanıkların ilk tedavisinde farkındalığı artırmaya yönelik öneriler sunmaktır. Bu tanımlayıcı-kesitsel çalışmaya 1 Kasım 2019 ile 31 Aralık 2019 tarihleri arasında üçüncü basamak yanık merkezi polikliniğine ilk kez başvuran ve katılmayı kabul eden 300 yanık hastası dahil edildi. Hasta verileri ve olay yerinde veya başka bir sağlık kuruluşunda uygulanan ilk tedaviler değerlendirildi. Çalışmaya katılan 300 hastanın %51'i erkek (n=153), %49'u (n=147) kadındı. Etiyolojide en sık çay (n=96) ve su (n=79) ile yanma görüldü. Yanık vücut alan yüzdesi 3,82±4,8 olarak bulundu. İlk müdahale %79 (n=237) hastada olay yerinde yapılırken, %21 (n=63) hastada bir sağlık kurumunda yapılmıştı. Olay yeri müdahalelerinden %73,8'i (n=175) uygun müdahale değildi. Sağlık kurumunda yapılan 63 müdahalenin %39,7'sinin (n=25) uygun olmadığı görüldü. Yanık polikliniğimize başvuran hastaların veya ebeveynlerinin yanıkta ilk yardım konusunda yeterince bilgileri olmadığı görüldü. Annelere yönelik eğitim programları ile ev içi çocuk yanık insidansında azalma ve doğru ilk müdahale konusunda farkındalık sağlanabilir. İş yerlerinde korunma ve doğru müdahale için ise iş sağlığı ve güvenliğiyle ilgili çalışmaların ciddiyetle sürdürülmesi gereklidir. Yanık ile ilgili sağlık kurumlarında yapılan uygulamalarda da eksiklikler olduğu saptandı. Bu konuda sağlık personeline hizmet içi eğitim verilmesinin faydalı olacağı düşünüldü.

Anahtar Kelimeler: Yanık; ilk tedavi; farkındalık;

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1. Introduction

First aid in burns are applications performed without seeking medical equipment at the scene to prevent the situation from getting worse until medical assistance is provided by healthcare professionals. It has been reported in many publications that appropriate first aid reduces pain, edema, and inflammation and contributes to wound healing (1-4). The first thing to do at the scene is to remove the heat source. Afterwards, clothes should be removed quickly to start cooling process. Cooling should ideally be done with approximately 15 degrees of water within 20 minutes after injury and should continue for 20 minutes (2,3,5). Use of ice water should not be applied as it will cause vasoconstriction and eventually progression of burns, as well as may cause hypothermia especially in children. It is sufficient to cover the burned area with a sterile cloth or a clean garment on the way to the health institution (4). The width and depth of the wound are evaluated once the patient is transferred to a health institution. Based on this evaluation, appropriate fluid resuscitation is initiated by opening the vascular access to the required patients and urinary monitoring is done with a Foley catheter. Any jewelry or clothes that will disrupt the circulation is removed (6). In first-degree burns, moisturizing creams are sufficient; the wound does not need to be covered. In second degree burns, the wound is closed with gauze impregnated with paraffin or oily cream. Silver sulfadiazine may be preferred in the initial treatment of burns but not for the face (2-4).The use of drugs that can lead to vasoconstriction should be avoided.

In this study, it was aimed to determine the first applications of the first and second degree burns at the scene or in the health institutions before admission to a burn center and to evaluate these interventions. In addition, the first steps to be taken in the burn and suggestions to raise awareness are presented.

2. Materials and Methods

A total of 300 patients admitted to our outpatient clinic of the Burn Center for the first time between 1 November 2019 and 31 December 2019 and accepted to participate in the study were included in the study. Electrical burns and burns with suspicion of inhalation are not included. A written consent was obtained from the participants. In this descriptive-cross-sectional study, the demographic data of the patients, the place where the burn injury happened, the etiology of the burn, the educational status of the participants, the first applications performed at scene or in the health institution were questioned. The percentage of burned total body surface area and hospitalization were also evaluated.

This study was approved by the local Clinical Research Ethical Committee of our Hospital (Decision no: 2019/585).

Statistical Analysis

Statistical Package for Social Sciences 20.0 for Windows was used for the analysis of the data. Results were expressed as mean (standard deviation) (min-max), n and percent.

3. Results

Between 1 November 2019 and 31 December 2019, 300 patients who admitted to our outpatient burn clinic for the first time and volunteered to participate were included in the study. Among the participants 51% of them were male (n=153) and 49% (n=147) were female. The mean age of the patients was 9.46±15.4 (min-max=0.5-79) years. The percentage of burned total body area (TBSA) was found to be 3.82±4.8 (min-max=1-37). Burn injuries happened indoors in 85.33% (n=256) of patients whereas 9.66% (n=29) happened in the open area and in the remaining 5% (n=15) at workplace. Among 29 injuries occurred at open areas, 25 of them occurred at the roof or garden of the house where there was easy access to a water source. Demographic and clinical data of the patients are given in Table 1.

Scald burns with water and tea were the most common cause of burns. The etiology of burns is summarized in Table 2.

Table 1. Demographic and clinical data of patients.

	Study Group (n=300)
Age (years)	9.46±15.4
Gender M/F (n)	153/147
Education Status	
Illiterate	59
Primary school	102
Secondary School	71
Higher Education	68
TBSA (%)	3.82±4.8
Hospitalization (Yes/No)	58/242

Values shown as mean±standard deviation, M/F= Male/Female, TBSA= Total Body Surface Area

Table 2. Etiology of burns.

Etiology	Study Group (n=300) n	%
Tea	96	32.0
Water	79	26.3
Contact	46	15.3
Meal	29	9.7
Flame	27	9.0
Milk	12	4.0
Oil	6	2.0
Chemical	5	1.7

In 79% (n=237) of the patients, the first intervention was performed at the scene, while in 21% (n=63) of patients in a medical institution. Approximately 73.8% (n=175) of the first interventions (such as water and ice application, centaury oil, yogurt, toothpaste) were not appropriate. Regarding doing nothing at the scene (n=63) also as an inappropriate intervention, 79.33% (n=238) of the first intervention were not appropriate. In addition the ideal cooling time, which should be 20 minutes, was applied by few patients or parents and some of them did not fully remember the cooling time with the rush also. For that reason a cooling time more than 10 minutes is accepted as an appropriate intervention. Only 62 (26.2%) of our patients were cooled properly. Although most of the patients or parents applied tap water as the first intervention, it was considered as an inappropriate intervention if the duration of cooling was less than 10 minutes. Our data about the first intervention at the scene is given in Table 3.

Table 3. First treatment at scene.

First Treatment	Patients (n=237)	
	n	%
Tap water	142	59.9
Water and ice	59	24.9
Centaury oil	13	5.5
Yoghurt	8	3.4
Tooth paste	6	2.5
Egg	3	1.3
Others	6	2.5

When the patients were questioned about the knowledge of first intervention in a burn injury, only 4 people who had experienced a burn injury before, and 3 people working in the heavy and dangerous work class category had satisfactory information. Other patients or parents did not have satisfactory knowledge regardless of their education.

When the interventions performed in a health institution were evaluated 60.3% (n=38) of them was appropriate and 39.7% (n=25) of them was not. Inappropriate interventions were the use of silver sulfadiazine to the face in 7 patients, the use of topical vasoconstrictors in 12 patients, and not dressing a second degree burn after applying antibiotic-containing cream to the wound.

4. Discussion

First aid in burn helps to reduce pain and burn damage (7). Most burns occur at home, at work, or in open areas around home. In other words, most burns occur at a distance within reach to a water source required for appropriate first aid. In this study, the information of the burn patients or their parents about first aid and the practices performed at the injury scene or in the health institution were examined and our results were compared with similar studies in the literature.

Burn wounds are sterile, but are susceptible to colonization quickly by bacteria. While the exudate in the environment acts like a culture medium, the application of unsuitable substances increases the risk of infection (8). Applications such as yogurt, toothpaste, tomato paste, egg whites, potatoes, oil, milk, urine and mud have been encountered in different publications (1,8-11). In our study, there were applications such as yogurt, toothpaste, egg whites, centaury oil and tar. Due to its easy availability in our region, the use of centaury oil is frequent. In a study on mothers' knowledge and behavior in home accidents, the level of knowledge was found to be higher in those with a high education level (12).

Improper practices in first treatment of burn result from lack of knowledge in the society. Studies conducted in many countries such as England, Wales, India and China found that there is about 3.7-32% accurate information about first aid in burns (7,10,13-15). While cooling the burned patient with the water was found as high as 82% but it was observed that the knowledge of proper duration for applying water decreased to 9% (7,10). In the studies conducted in our country, it was stated that water was used in the first intervention at the rate of 39.6% - 64%, but the duration for applying water was not specified (8,11). In our study, it was seen that 59.9% of the first intervention was cooling with water, but the correct intervention rate decreased to 26.2% considering the duration of time for applying water. In a study conducted at a university hospital in Wales, 32% of the participants were found to have correct first aid information for burns. The high rate found in the study has been attributed to the fact that 40% of the participants took compulsory basic first aid training at the workplace (13). In our study, 3 people who burned in the workplace in the heavy and dangerous business class category had knowledge about the first intervention in a burn injury and they applied

the proper intervention. In some studies the participants were questioned about their source of information on first aid in burns. They mostly stated the internet (32.9-79%), and to a lesser extent, other sources of information (health book, television, friends and health institutions) (7,16). In a meta-analysis examining the information about first aid in burns on the internet, Burgess et al. concluded that these contents were wrong, inadequate and inconsistent (17). Since the internet is mostly used to access information today, the correct information should be conveyed by the experts of the subject.

In a study on childhood burns and parenteral awareness the authors stated that 20% of the patients were referred to a burn center without performing any medical intervention in the health institution and some patients were referred without dressing a second degree burn (11). In our study, we also found that the first aid practices performed to 39.7% of the patients who admitted to a health institution other than a burn unit or center was not sufficient.

In a cross-sectional study in which first aid information determinants were examined in burns, it was observed that individuals who went to a first aid course gave 15% more correct answers to the questionnaire and those who took the course in the last five years had a higher rate of correct answers (18). After a multimedia campaign in New Zealand, it was observed that first aid information increased and hospitalization of burn patients decreased (19). In a systematic review evaluating the publications related with attempts to increase the level of education, it was found that there was an increase in the level of knowledge and a decrease in harmful traditional practices with initiatives such as media campaigns and face-to-face education (20). In a study conducted in India, the results of the "community awareness program" and "school education programs", which span over a 5-year period, were discussed. Auditory and visual methods or face-to-face training were used to inform about in-kitchen arrangements, cooking on the floor, the way of dressing during cooking and the use of electrical tools. The results of the programs were satisfactory (14).

5. Conclusion

In conclusion it was observed that the patients or their parents who admitted to our outpatient burn clinic did not have enough information about first aid in burns. For this reason, with the training programs for parents, awareness can be raised about burns in the house and appropriate first treatment. Education and controls related to occupational health and safety must be taken seriously in work places to ensure protection and correct intervention at work. First aid courses should be organized at schools either. It is thought that it would be beneficial to provide in-service training to health personnel in order to eliminate the deficiencies in the practices performed for burns in health institutions.

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Research Article / Araştırma Makalesi

The Usefulness of Pleural Lactate Measurement for Differentiating Transudate and Exudate

Transuda ve Eksüdayı Ayırt Etmek İçin Plevral Laktat Ölçümünün Kullanılabilirliği

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Abstract

Our study aimed to evaluate pleural lactate levels, to identify the reliability and validity of determining pleural fluid quality in patients with pleural effusion.This is a prospective, observational study conducted on patients who were admitted to a university hospital between July 1, 2017, and January 31, 2018, and diagnosed with pleural effusion. Pleural fluid classification into transudates and exudates was made according to Light's criteria. The study group consisted of a total of 169 patients with pleural effusion, [99 (58.6%) male and aging 18-93 years (mean ± SD, 64.6 ± 16.1 years)]. Forty-four (26%) of the patients were evaluated as exudate and 125 (74%) as transudate. The median value of lactate was 3.20 mmol/L (min-max: 0.90-14.3) in exudate patients and 1.85 mmol/L (min-max: 0.90-4.70) in transudate patients, and a significant difference was detected in the comparison of both (z: 5.894; p<0.001). There was a positive correlation between pleural lactate levels and pleural LDH, pleural LDH/serum LDH and pleural protein/serum protein ratios. The cut-off value of the pleural fluid lactate level was determined to be 2.0 for the highest sensitivity and specificity (sensitivity: 85%, specificity: 64%; AUC: 0.799). Measurement of lactate levels in pleural fluid can be useful for the differentiation of transudate and exudate fluid. Moreover, detection of lactate levels in a very short period may provide a more useful screening tool compared to other strategies.

Keywords: transudate-exudate, pleural lactate

Özet

Çalışmamız, plevral efüzyonlu hastalarda transüda ve eksüdayı ayırt etmenin güvenilirliğini ve geçerliliğini belirleyerek plevral laktat düzeylerini değerlendirmeyi amaçladı.1 Temmuz 2017 ile 31 Ocak 2018 tarihleri arasında bir üniversite hastanesine başvuran ve plevral efüzyon tanısı alan hastalar üzerinde yapılan prospektif, gözlemsel bir çalışmadır. Transüda ve eksüda plevral sıvı sınıflandırması Light kriterlerine göre yapılmıştır. Çalışma grubu pevral effüzyonlu toplam 169 hastadan oluştu [99 (% 58.6) erkek ve 18-93 yaş arası (ortalama ± SS, 64.6 ± 16.1 yıl)]. Hastaların 44'ü (% 26) eksüda ve 125'i transüda olarak değerlendirildi. Laktatın ortanca değeri eksüda hastalarda 3.20 mmol / L (min-maks: 0.90-14.3) ve transüda hastalarda 1.85 mmol / L (min-maks: 0.90-4.70) idi ve her ikisinin karşılaştırılmasında anlamlı farklılık saptandı. (z: 5.894; p <0.001). Plevral laktat seviyeleri ile plevral LDH, plevral LDH / serum LDH ve plevral protein / serum protein oranları arasında pozitif bir korelasyon tespit edildi. En yüksek duyarlılık ve özgüllük için plevral sıvı laktat düzeyinin kestirim değeri 2.0 olarak belirlendi (duyarlılık:% 85, özgüllük:% 64, AUC: 0.799). Plevral sıvıda laktat seviyelerinin ölçümü, transüda ve eksüda sıvısının ayrımı için yararlı olabilir. Ayrıca laktat seviyesinin çok kısa sürede tespiti diğer stratejilere göre daha kullanışlı bir tarama aracı olarak kullanılabilir.

Anahtar Kelimeler: transuda-eksuda, plevral laktat

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1. Introduction

Pleural effusion is one of the common pulmonary emergencies (1). It is defined as an accumulation of abnormal fluid in the pleural space and may occur for many different causes (2). The incidence of pleural effusion, which can occur as a complication of various diseases, is 3-5 cases per 1000 people per year (3) and the mortality rate is 0.3 per 100.000 (4). Etiology varies according to many factors like age, living area, and the quality of the diagnostic and therapeutic methods. Although many advances are made in the medical field and new diagnostic tools have emerged, about 20% of the cases cannot be diagnosed (5). The first step in the etiologic diagnosis of a pleural effusion is to differentiate a transudate from an exudate. A delayed etiological diagnosis can be associated with higher morbidity and mortality therefore the determination of pleural fluid characteristics is important for management and treatment. The pleural fluid analysis yields important diagnostic information in pleural effusions. If pleural fluid is detected as exudate, additional tests are required to determine the etiology, if the fluid is transudate, further diagnostic procedures are not required and a treatment plan is made according to the underlying disease (6). The most commonly used method for determining pleural fluid characteristics is Light's criteria, which is based on the pleural fluid and serum protein-LDH measurements (7). Despite its high sensitivity, Light's criteria are not sufficient for the diagnosis of all pleural fluids. Therefore, in addition to Light's criteria, different parameters have been used recently, such as serum-pleural fluid albumin gradient (8), pleural fluid cholesterol level (9), Costa criteria (10), Köktürk formula (11). Pleural lactate is one of them, but the number of studies in the literature is limited to a few (12-15).

The aim of this study is to investigate the diagnostic accuracy of the measurement of lactate level in pleural effusion and assess the validity and reliability of the pleural fluid characteristics by using Light's criteria.

2. Materials and Methods

Study design and setting

This prospective study was conducted in patients who were admitted to University Health Practice and Research Hospital (Emergency Service and Chest Diseases Clinics) between July 1, 2017, and January 31, 2018. One hundred sixty-nine patients with pleural effusion were included in the study. The study was conducted in accordance with the revised Declaration of Helsinki and was approved by the Research Ethics and Review Board of the University Medical Center (Reference Number-Date: 03-29.06.2017). Also, written permission has been obtained by all participants. For the recruitment of patients, the following inclusion criteria were used: age 18 years or older, patients with pleural effusion and patients who underwent thoracentesis. Exclusion criteria were: pregnant, traumatized, unable to perform thoracentesis and bleeding diathesis. Pleural effusion was confirmed by a thorough physical examination and a postero-anterior or lateral chest radiograph and ultrasonography. Pleural fluid classification into transudates and exudates was made according to Light's criteria

Data source and collection

Information on socio-demographics (age, gender, level of education, etc.), past medical history, comorbidities, drug history, vital signs were recorded.

After obtaining the written consent from patients, thoracentesis was performed and pleural fluid was analyzed for biomarkers (protein, albumin, LDH and lactate). Simultaneous blood sample protein, LDH and albumin levels were also obtained. In the study, the thoracentesis procedure was performed with ultrasound (USG). Pleural fluid removal with USG was performed by trained doctors with static and dynamic methods according to the clinical condition of the patient. Fluid obtained by thoracentesis

was taken into biochemistry tube for protein, albumin, glucose, cholesterol, LDH, and heparinized insulin injector for pleural fluid lactate level and pH. Lactate and ph values were analyzed with the ABL800 BASIC blood gas device. Pleural fluid protein, LDH, glucose, cholesterol and albumin levels were analyzed in the biochemistry laboratory with the device named Cobas 6000 C501. Protein, LDH, glucose, cholesterol and albumin levels from venous blood samples obtained simultaneously were studied in the biochemistry laboratory with the Cobas 6000 C501 device.

Statistical analysis

Data were analyzed using IBM SPSS (version 20.0). A Chi-square test was used for univariate analyzes to determine the variables associated with pleural fluid characteristics. The Shapiro-Wilk test was used to test the normal distribution of the non-categorical data obtained from the pleural fluid analysis. Mann-Whitney U test was used for comparison of the pleural fluid characteristics and measurement data. To differentiate transudate-exudate, the predictive value of pleural lactate levels (by accepting Light's criteria as a standard), predictive value and area under the ROC curve (AUC) were calculated by using the MedCalc (v18.2.1) software. According to predictive value for pleural lactate level, pleural fluid levels of patients were re-classified as transudate and exudate. Then, sensitivity (a/a+c), specificity (d/d+c), positive predictive value (a/a+b), negative predictive value (d/d+c) and accuracy ratio (a+d/a+b+c+d) were calculated according to Light's criteria (16). Later, the definitive diagnoses of the patients were recorded on the questionnaire and sensitivity-specificity of the Light's criteria were calculated according to these definitive diagnoses.

3. Results

A total of 169 patients, [99 (58.6%) male and ageing 18-93 years (mean ± SD, 64.6 ± 16.1 years)] were included in the study. Most commonly seen comorbidities were chronic diseases in 86 (50.3%), malignancy in 50 (29.4%), CHF in 29 (17.1%), CRF in 12 (7%), chronic liver disease (CLD) in 4 (2.3%) cases. Used drugs were diuretics in 29.6%, antibiotics in 5.9% and beta-blockers in 26.6% of cases.

According to Light's criteria, 44 (%26) of the patients were evaluated as transudate and 125 (%74) as exudate. In the relationship between pleural fluid content and variables; exudative pleural effusion was observed in patients younger than 60 years (p=0.036), having a high fever (p=0.045), transudative pleural effusion was observed in patients with a past medical history of CHF and CRF (p≤0.0001, p=0.003, respectively). Comparison of characteristics according to pleural fluid content Table 1.

Table 1. Comparison of demographic, vital signs, comorbidities and drug use according to pleural fluid characteristics

Characteristics		n (%)	Quality of pleural fluid		Statistical analysis x^2; p
			Transudate n: 44 (%)	Exudate n: 125 (%)	
Age group (year)	≤59	47 (27.8)	7 (14.9)	40 (85.1)	6.663; 0.036*
	60-69	38 (22.5)	8 (21.1)	30 (78.9)	
	≥70	84 (49.7)	29 (34.5)	55 (65.5)	
Gender	Male	70 (41.4)	24 (24.2)	75 (75.8)	0.206; 0.650*
	Female	99 (58.6)	20 (28.6)	50 (71.4)	
SBP	Normal	43 (25.4)	8 (18.6)	35 (81.4)	1.177; 0.232*
	Abnormal	126 (74.6)	36 (28.6)	90 (71.4)	
Pulse	Normal (60-100 beat/ min)	81 (47.9)	23 (28.4)	58 (71.6)	0.245; 0.620*
	Abnormal	88 (52.1)	21 (23.9)	67 (76.1)	
RR	Normal (12-20 resp/min)	54 (32.0)	13 (24.1)	41 (75.9)	0.044; 0.834*

	Abnormal	115 (68.0)	31 (27.0)	84 (73.0)	
Body temperature	Normal (36,5-37,5ºC)	151 (89.3)	43 (28.5)	108 (71.5)	0.045**
	Abnormal	18 (10.7)	1 (5.6)	17 (94.4)	
CHF/CRF/CLD	Present	38 (22.5)	18 (13.7)	113 (86.3)	42.939; <0.001*
	Absent	131 (77.5)	26 (68.4)	12 (31.6)	
Malignancy	Present	50 (29.6)	10 (20.0)	40 (80.0)	0.935; 0.334*
	Absent	119 (70.4)	34 (28.6)	85 (71.4)	
Chronic disease	Present	86 (50.9)	30 (34.9)	56 (65.1)	6.214; 0.013*
	Absent	83 (49.1)	14 (16.9)	69 (83.1)	
Diuretic use	Present	50 (29.6)	26 (52.0)	24 (48.0)	22.981; <0.001*
	Absent	119 (70.4)	18 (15.1)	101 (84.9)	
B blocker use	Present	45 (26.6)	22 (48.9)	23 (51.1)	5.056; <0.0001*
	Absent	124 (73.4)	22 (17.7)	102 (82.3)	
Antibiotic use history	Present	10 (5.9)	0 (0.0)	10 (100.0)	0.065**
	Absent	159 (94.1)	44 (27.7)	115 (74.0)	

* *Chi-Squared test* ***Fisher's Exact Test , SBP: Systolic blood pressure, RR: Respiratory rate, CHF: Chronic Heart Failure, CRF: Chronic Renal Failure, CLD: Chronic Liver Disease*

Comparison of pleural protein and LDH, albumin gradient, plasma protein and LDH ratio between transuda and exuda fluids are given in Table 2.

Table 2. Parameters used for differentiating transudates and exudates

Parameters		**Quality of Pleural effusion**		**Statistical analysis**
		Transudate n (%)	Exudate n (%)	**x^2; p**
Pleural protein	<3 g/dl	26 (59.1)	5 (4.0)	62.316; <0.001
	≥3 g/ dl	18 (40.9)	120 (96.0)	
Pleural LDH	<200 IU	42 (95.5)	26 (20.8)	72.355; <0.001
	≥200 IU	2 (4.5)	99 (79.2)	
Albumin gradient	<1.2	4 (9.1)	77 (61.6)	33.881; <0.001
	≥1.2	40 (90.9)	48 (38.4)	
PSPR/S_PR	<0.5	32 (72.7)	9 (7.2)	72.526; <0.001
	≥0.5	12 (27.3)	116 (92.8)	
PSLDH/S_LDH	<0.6	42 (95.5)	26 (20.8)	72.355; <0.001
	≥0.6	2 (4.5)	99 (79.2)	

After pleural fluid differentiating according to the Light criteria, the median value of lactate was 3.20 mmol/L (min-max: 0.90-14.3) in exudate patients and 1.85 mmol/L (min-max: 0.90-4.70) in transudate patients, and a significant difference was detected in the comparison of both (z: 5.894; p<0.001).

There was a positive correlation between pleural lactate levels and pleural LDH, pleural LDH/serum LDH and pleural protein/serum protein ratios (Table 3).

Table 3. Correlation between lactate and Light cirteria parameters

	Pleural LDH level r; p	**Pleural LDH/serum LDH ratio r; p**	**Pleural protein/serum protein ratio r; p**
Pleural lactate level	**0.656; 0.000**	**0.611; 0.000**	**0.419; <0.001**

The predictive value of pleural fluid lactate level was determined to be 2.0 for the highest sensitivity and specificity [sensitivity: 85%, specificity: 64%, positive likelihood ratio: 2.3 (CI: 1.6-3.5), negative likelihood ratio: 0.24 (CI: 0.1-0.4), the area under the curve: 0.799 (CI: 0.7-0.9)] (Table 4, Figure 1).

Table 4. Comparison of lactate for differentiating transuda exuda

	Cutt-off value	Sensitivity %	Spesificity %	LR (+) CI	LR (-) CI	AUC CI
Pleural Lactate level	2.0 mmol/L	85	64	2.33 (1.6-3.5)	0.24 (0.1-0.4)	0.799 (0.7-0.9)***

: CI= %95 confidence interval; AUC: Area Under Curve

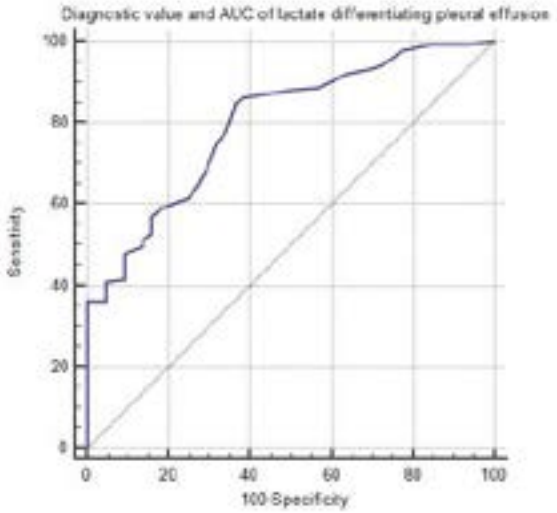

Figure 1.

4. Discussion

The results of our study show that the diagnostic parameters of Light's criteria are strongly positively correlated with pleural lactate levels. The best advantage of lactate levels measurements is that the result can be achieved in a very short time after the invasive thoracentesis procedure. These advantages may be important in septic cases due to pneumonic effusion where a prompt treatment decision is required. Therefore this potentially enables rapid decision-making at the time of the initial diagnosis. However, further investigations are needed to differentiate between these two groups.

Increased production or decreased absorption causes pleural fluid accumulation and its pathophysiology changes depending on the underlying disease. History and physical examination of a patient with pleural effusion can give an idea of the nature of the fluid. Then, diagnosis can be confirmed with parameters obtained by thoracentesis. Various parameters are used to differentiate transudative and exudative pleural effusion, but there is no exact method of sensitivity and specificity (17, 18). Light's criteria, although more than 40 years have passed, is accepted as the standard and the first step in discrimination of transudate and exudate (19). Different studies reported different sensitivity-specificity values for the Light's criteria (20, 21). The decrease in specificity rather than the sensitivity of Light's criteria

suggests that this can be changed with any modification.

Lactate is the end product of the anaerobic metabolism of pyruvate, catalyzed by lactate dehydrogenase and can be measured using a blood gas analyzer. Several recent studies evaluated lactate levels in biologic fluids such as ascites, pleural, synovial, and cerebrospinal fluid and its correlation to bacterial infections, empyema, autoimmune diseases, tuberculosis, hypovolemia and neoplastic diseases (12, 22-25). Lactate formation during infection is likely from bacterial metabolisms and results from high metabolic activities of the inflammatory cell population (26). However transudative pleural effusions are commonly caused by increased hydrostatic pressure or reduced plasma oncotic pressure, this may explain the low level of pleural lactate which is associated with minimal inflammatory and metabolic activities.

In their series of 118 cases, Yeo et al. Found that the mean lactate level of patients with transudative pleural fluid was lower than that of exudate fluids. With a ratio and cut-off value similar to our study, they found the cut-off value for pleural lactate as 2.50 mmol / L, the sensitivity as 77.78% and the specificity as 54.17% for the distinction between transudate and exudate (19).

Therefore we hypothesized that pleural fluid lactate can help us in differentiating exuda and transude in our patient. As a result, in our study pleural lactate level could be used in transudate-exudate discrimination, when the cut-off value of pleural lactate was taken as 2 mmol / L (Light's criteria were accepted as a standard) sensitivity was found to be 61.3% and specificity was found to be 86.4%.

Limitations

The present study has some limitations. First of all our study is single centered and our sample is small to clearly define the diagnostic role of lactate in pleural effusion and its real clinical use

5. Conclusion

Light's criteria are commonly used parameters in the differentiation of transudate-exudate. Pleural lactate measurement after thoracentesis is quickly and very easy and simple methods that can lead to the physicians working in emergency services. We concluded that pleural lactate could be useful in practice and can be used in the differential diagnosis. We also think that multicenter and more comprehensive studies may be useful in determining the role of pleural lactate in differentiating transudate exudate effusions.

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Research Article / Araştırma Makalesi

İnme Hastalarında Robot Destekli Üst Ekstremite Eğitiminin El Fonksiyonu ve Yaşam Kalitesi Üzerine Etkisi

The Effect of Robot-Assisted Upper Extremity Training on Hand Function and Quality of Life in Stroke Patients

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Özet

Çalışmanın amacı, inmeli hastalarda geleneksel rehabilitasyona ek olarak uygulanan robot destekli üst ekstremite eğitiminin el fonksiyonu ve yaşam kalitesi üzerine etkisini araştırmaktı. Çalışmaya katılmaya gönüllü toplam 49 kronik inmeli hasta dahil edildi. Tüm hastalar geleneksel rehabilitasyon programına ek olarak günde 30 dakika, haftada 5 kez, 6 hafta boyunca ArmeoSpring üst ekstremite robotik cihazı ile eğitime katılan hastaların geçmişe yönelik bilgileri kayıt edildi. Hastaların başlangıçta ve tedavi sonunda el fonksiyonları ABILHAND İnme El Fonksiyonu anketi ve yaşam kaliteleri ise İnme Etki Ölçeği 3.0 (İEÖ) kullanılarak değerlendirildi. Çalışmaya katılan inmeli hastaların %57,2'si kadın ve yaş ortalamaları 51,6±11,1 yıl idi. İnmeden sonra geçen süre ortalamaları ise 3,1±1,7 yıl idi. Eğitimden sonra hastaların ABILHAND İnme El Fonksiyonu skorlarında istatistiksel olarak anlamlı iyileşme olduğu saptandı (p=0,0001). Ayrıca, İEÖ 3.0'ın el fonksiyonu (p=0,0001) ve günlük yaşam aktiviteleri (p=0,0001) alanları başta olmak üzere tüm alanlarda anlamlı düzeyde gelişme olduğu bulundu (p<0,05). Geleneksel rehabilitasyon programı ile kombine edilmiş robot destekli üst ekstremite eğitiminin inmeli hastaların el fonksiyonlarını ve özellikle günlük yaşam aktivitelere katılımlarını artırarak yaşam kalitelerini iyileştirdiği görüldü.

Anahtar Kelimeler: İnme, robotik rehabilitasyon, üst ekstremite, fonksiyon, yaşam kalitesi

Abstract

The aim of the study was to investigate the effects of robot-assisted upper extremity training on hand function and quality of life in stroke patients. A total of 49 chronic stroke patients who volunteered to participate in the study were enrolled. In addition to the traditional rehabilitation program, all patients received upper extremity training with the ArmeoSpring robotic device for 30 minutes a day, 5 times a week, for 6 weeks. Hand functions of the patients at the baseline and at the end of the treatment were evaluated using the ABILHAND Stroke Hand Function Questionnaire and their quality of life using the Stroke Impact Scale 3.0 (SIP). A 57.2% of the stroke patients participating in the study were female and the mean age was 51.6±11.1 years. The mean time after stroke was 3.1±1.7 years. A statistically significant improvement was found in the ABILHAND Stroke Hand Function Questionnaire scores of the patients after the training (p=0.0001). In addition, it was found that there was a significant improvement in all areas, especially hand function (p=0.0001) and activities of daily living (p=0.0001) of SIP 3.0. It was observed that robot-assisted upper extremity training combined with the traditional rehabilitation program improved the quality of life of stroke patients by increasing their hand functions and especially their participation in daily life activities.

Keywords: Stroke, robotic rehabilitation, upper limb, function, quality of life

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1. Giriş

İnme olarak adlandırılan serebrovasküler olay, ciddi ve yaygın bir sağlık sorunudur. Dünyada birçok ülkede ikinci veya üçüncü en yaygın ölüm nedenidir ve hayatta kalanların bağımsızlığını ve yaşam kalitesini önemli ölçüde etkilemektedir (1). Dünya genelinde her yıl yaklaşık olarak 13,7 milyon kişi inme geçirmekte, 5,5 milyon kişi bu nedenle hayatını kaybetmekte ve 5 milyon kişide inme sonrası yaşamları boyunca kalıcı motor etkilenim meydana gelmektedir (2). Ülkemizde ise 2018 yılındaki toplam ölümlerin %22,4'ünün serebrovasküler olaydan kaynaklandığı bildirilmiştir. Hastaların %20'si erken dönemde olmak üzere yaklaşık %30'u bir yıl içinde hayatını kaybettiği, hayatta kalanların üçte birinin ise günlük yaşam aktivitelerinde bağımlı hale geldiği rapor edilmiştir (3).

İnme sonrası üst ekstremite alt ekstremiteye göre daha çok etkilenmekte olup motor iyileşme üst ekstremitede daha zayıf olmaktadır. İnmeli hastalarda tedavi ile kazanılan fonksiyonel bağımsızlık düzeyinin üst ekstremite ve el motor bozukluğu ile büyük oranda ilişkili olduğu bildirilmiştir (4). İnmeli hastaların yaklaşık %30 ila %66'sı kas güçsüzlüğü, spastisite, sensorimotor yetersizlikler nedeniyle üst ekstremite kalıcı fonksiyon kayıplarına bağlı olarak günlük yaşam aktivitelerinde etkilenen ekstremitelerini kullanamamaktadır bu durum hastaların yaşam kalitelerini etkilemektedir (5, 6). Üst ekstremite fonksiyonu ile yaşam kalitesinin direkt ilişkili olduğu, üst ekstremiteye yönelik uygulamaların yaşam kalitesinde belirgin gelişmelere neden olduğu bildirilmektedir (6). İnmeli bireylerin günlük yaşam aktivitelerini bağımsız olarak katılmaları için el motor fonksiyonlarının en uygun şekilde restore edilmesi önemlidir. Hastaların %15'inden daha azında üst ekstremite normal motor fonksiyonunu geri kazanmaktadır (7). Günümüzde inme rehabilitasyonunda yaygın olarak uygulanan tedavi yöntemleri olarak konvansiyonel yöntemler (eklem hareket açıklığı egzersizleri, kuvvetlendirme, germe, ortezleme ve mobilizasyon yöntemleri), nörofizyolojik yaklaşımlar, motor öğrenme yöntemleri, proprioseptif nöromusküler fasilitasyon teknikleri, fonksiyonel elektriksel stimülasyon, transkraniyal manyetik stimülasyon ve biofeedback'i içine alan birçok yöntemler kullanılmaktadır (8).

Serebral plastisite ve motor öğrenmeyi geliştirmek amacıyla son yıllarda geleneksel tedavilere ek olarak, robot destekli tedavi, video oyun eğitimi, sanal gerçeklik gibi teknoloji temelli rehabilitasyon programları da özellikle üst ekstremite rehabilitasyonunda kullanılmaya başlanmıştır (9, 10). Robotik cihazların rehabilitasyonda kullanılması, etkilenmiş üst ekstremiteye yüksek yoğunluklu, bol tekrarlı, görev odaklı ve interaktif bir tedavi seçeneği sunmaktadır. Robot destekli eğitimin sahip olduğu sanal gerçeklik veya oyun sistemi katılımcıların motivasyon düzeyini ve eğitim programlarına katılımını artırmaktadır (11, 12). Robot destekli eğitimle hastalar eğlenirken aynı zamanda da tedavi olmaktadırlar. Bu yöntem çoğu zaman aktif katılım gerektirse de klasik tedavilerde tamamlayıcı bir biçimde kullanılarak hastaya büyük bir fayda sağlamaktadır (13). Literatürde robot destekli eğitimin omurilik yaralanmalı hastalar (14-16) başta olmak üzere inmeli hastalarda üst ekstremite motor fonksiyonları ve günlük yaşam aktiviteleri üzerine etkilerini araştıran kısıtlı sayıda çalışma olmasına rağmen yaşam kalitesi üzerine etkisini araştıran çalışmaya rastlanmamıştır (17-20). Bu nedenle çalışmamızın amacı, inmeli hastalarda geleneksel rehabilitasyona ek olarak uygulanan robot destekli üst ekstremite eğitiminin el fonksiyonu ve yaşam kalitesi üzerine etkisini araştırmaktı.

2. Gereç ve Yöntemler

İnme tanısıyla kabul edilen ve yatılı olarak tedavi gören ve en az altı hafta üst ekstremite robotik rehabilitasyon eğitimi almış hastalar retrospektif olarak tarandı. Çalışmaya dahil edilme kriterleri, serebral kanama veya serebral enfarktüs nedeniyle yatarak rehabilitasyon almış olmak ve değerlendirme parametreleri ile ilgili verilerin mevcut olması idi. Retrospektif analiz için hasta seçim

kriterleri aşağıdaki gibiydi; a) 18 yaş ve üzeri olma, b) en az bir yıl önce inme geçirmiş olma, c) Modifiye Ashworth Skalası'na göre spastisite skoru dirsek, el bileği ve parmak fleksör kaslarında 2 ve altında olma, d) son 6 ay içinde Botulinum toksin A enjeksiyonu yapılmamış olma ve geleneksel rehabilitasyon programına ek olarak en az en az 30 seans robot destekli üst ekstremite eğitimine katılmış olma idi. İnme dışı nörolojik hastalık nedeniye yatış yapmış olmak, Nöromüsküler Elektrik Stimülasyonu (NMES) veya fonksiyonel elektrik stimülasyonu almış olmak, değerlendirme verilerinde eksiklik olmak ve 30 seanstan daha az üst ekstremite robot destekli eğitime katılmış olmak çalışmadan dışlanma nedeni olarak belirlendi. Çalışma etik onayı Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulunun 19.06.2017 tarih ve 2017-06-22 izin kararı ile alındı. Çalışma Helsinki Deklerasyonu'na uygun olarak yürütüldü.

Çalışmaya dahil edilme kriterlerine uygun olan hastalara ait cinsiyet, yaş, boy, kilo, eğitim durumu gibi kişisel bilgiler ve inme süresi, inme tipi, etkilenen taraf gibi klinik değerlendirmeler ilk seansta sorgulanarak kaydedildi. Altı haftalık tedavi programının başında ve sonunda el fonksiyonlarını değerlendirmek için ABILHAND İnme El Fonksiyonu Anketi (21, 22), yaşam kalitesini değerlendirmek için ise İnme Etki Ölçeği 3.0 kullanıldı (23, 24).

ABILHAND İnme El Fonksiyonu Anketi

Çalışmada hastaların el fonksiyonlarını sorgulamak amacıyla Penta ve arkadaşları (22) tarafından geliştirilen ABILHAND İnme El Fonksiyonu Anketi kullanıldı. Ankette hastaların beslenme, giyinme, ev isleri gibi günlük isleri gerçekleştirmede hastanın algıladığı zorluk derecesi sorgulanmaktadır. Ankette yer alan tek ya da çift el ile gerçekleştirilen 56 adet görev için hastanın kendisinden son bir aya yönelik olarak imkansız (0 puan), zor (1 puan) ve kolay (2 puan) şeklinde olan seçeneklerden kendisi için uygun olanı bildirmesi istendi. Yüksek puanın daha iyi el fonksiyonu anlamına gelmektedir. Anketin inme geçirmiş hastaların üst ekstremite el becerisini ölçmek üzere kullanılmasına yönelik çalışma yapılmıştır (21). Anketin henüz ülkemizde inmeli hastalar üzerinde yapılmış ve yayınlanmış güvenilirlik ve geçerlilik çalışmasına rastlanmamıştır.

İnme Etki Ölçeği 3.0

Çalışmada hastaların yaşam kaliteleri Duncan ve arkadaşları (25, 26) tarafından geliştirilmiş, geçerlilik güvenilirlik çalışmaları yapılmış İnme Etki Ölçeği 3.0 ile değerlendirildi. Bu ölçek 8 alt bölüm (kuvvet, el fonksiyonu, günlük yaşam aktiviteleri, mobilite, iletişim, duygu, hafıza ve katılım) ve 59 sorudan oluşmaktadır. Her bir soru, son bir hafta içinde yaşanan zorluğun 5 puanlı skala üzerinden değerlendirilmesi ile puanlanır. Her bir bölüm için skor 0-100 arasında değişmektedir. Ayrıca 8 alt bölüme ek olarak inme sonrası iyileşme algısının 0-100 puanlık görsel analog skala (0: Hiç iyileşme yok, 100: Tam iyileşme) ile değerlendirmesini içermektedir. Ölçeğin Türk toplumundaki inmeli hastalar üzerinde güvenilirlik ve geçerlilik çalışması Hantal ve arkadaşları (24) tarafından yapılmıştır.

Uygulanan Rehabilitasyon Programı

Geleneksel rehabilitasyon programı

Hastalar hastanede yatarak tedavi gördükleri geleneksel rehabilitasyon programında üst ekstremite fonksiyonelliğini artırmaya yönelik olarak; üst ekstremiteye yönelik ağırlık aktarma, uzanma, ağırlık taşıma, kaldırma, kaba ve ince kavrama aktiviteleri ve sık kullanılan objeleri manipule edilmesini çeşitli şekil ve büyüklükteki objeler ile çalışılarak hastaların problem yaşadığı alanlardaki sorunların çözülmesine yönelik günlük yaşam aktivitelerinde sık kullanılan aktiviteler seçilerek üst ekstremite fonksiyonelliğinin yeniden kazanılması hedeflendi. Ayrıca üst ekstremite kaslarına yönelik germe, kuvvetlendirme ve dayanıklık egzersizleri uygulandı. Tüm bu geleneksel rehabilitasyon programı günde 45 dakika, haftada 5 gün ve 6 hafta boyunca uygulandı.

Robot Destekli Üst Ekstremite Eğitimi

Son yıllarda görülen teknolojik gelişmelerle paralel olarak sağlık alanında da hastaların rehabilitasyon programlarına katkı sağlamaları açısından robotik cihazların kullanımı giderek yaygınlaşmıştır. Bu alanda yapılan çalışmalar robot destekli üst ekstremite eğitiminin inme sonrası nöral ağların organizasyona ve fonksiyonel motor becerilerin iyileşmesine olumlu katkıları olabileceğini ileri sürmektedir (27, 28). Literatürde geleneksel rehabilitasyon uygulamalarına kıyasla, robotik rehabilitasyonun tekrar, performansa dair geri bildirim ve motivasyon sağlaması gibi avantajları hastaların tedaviye katılımlarını artırdığı bildirilmiştir (29-31). Hastalar bilgisayar ekranında oluşturulan sanal ortam oyunları içerisinde hasta kendi elinin simülasyonunu görebilmekte ve ekrandaki objeleri omuz, dirsek ve el bileğini belirli açılarda pozisyonlarda tutarak el ile taşıma, tutma, sıkma, bırakma, kavrama gibi aktiviteleri gerçekleştirebilmektedir. Çalışmamızda ArmeoSpring üst ekstremite robotik cihazı kullanılarak günde 30 dakika, haftada 5 gün, 6 hafta boyunca basitten zor seviyeye doğru ilerleyen 6 farklı oyun ile üst ekstremite eğitimine katıldılar. Oyunlar ile omuz abdüksiyon-adduksiyon ve fleksiyon-ekstansiyonu, bilek fleksiyonu-ekstansiyonu, önkol supinasyonu-pronasyonu ve joystik kavrama ve bırakma ile el hareketleri teşvik edildi (Şekil 1).

Şekil 1. Robot destekli üst ekstremite eğitimde uygulanan oyun örnekleri

İstatistiksel Analiz

Çalışmada elde edilen verilerin analizinde "SPSS (Statistical Package for Social Sciences) (SPSS 22.0, SPSS, Chicago, IL)" istatistik programı kullanıldı, $p<0,05$ (iki yönlü) olan değerler istatistiksel olarak anlamlı kabul edildi. Çalışma verilerinin normal dağılımı gösterip göstermediği Shapiro-Wilk testi kullanılarak değerlendirildi. Çalışma verilerinin normal dağılıma uygun olduğu saptandı. Çalışmanın istatistiksel analizinde, değerlendirmeye alınan değişkenler en az, en çok, ortalama (Ort), standart sapma (SS) ve yüzde (%) değerleri ile tanımlandı. Hastaların tedavi öncesi ve sonrası ABILHAND İnme El Fonksiyonu Anketi ve İnme Etki Ölçeği 3.0 puanlarının karşılaştırılmasında Bağımlı Gruplar t-Testi kullanıldı.

3. Bulgular

Çalışmaya katılmaya gönüllü toplam 56 hasta dahil edilme kriterlerine göre değerlendirildi. Değerlendirilen hastalardan 5 hasta kriterlere uygun olmadığı (3 hastanın Modifiye Ashworth Skalası'na göre spastisite skoru 3 ve üzeri idi, diğer 2 hastada ise kontraktür gelişmişti), 2 hasta ise erken taburculuk nedeniyle çalışma dışı kamıştır. Çalışma 49 hasta ile tamamlanmıştır. Araştırmaya katılmış olan hastaların sosyo-demografik özellikleri incelendiğinde; çalışmaya katılan

hastaların %57,2'si kadın, yaş ortalamaları 51,6±11,1 yıl ve beden kitle indeksi ortalamaları 26,1±4,4 kg/m2 idi. Hastaların %42,9'u ilköğretim mezunu ve %57,2'si sol ekstremite etkilenimine sahipti. Hastaların etyolojisi incelendiğinde %71,5'inin iskemik serebrovasküler olay geçirdiği görüldü.

Hastaların inmeden sonra geçen süre ortalamaları 2,8±1,5 yıl idi (Tablo 1). Hastaların altı haftalık geleneksel rehabilitasyona ek olarak uygulanan üst ekstremite robotik eğitim sonrası ABILHAND İnme El Fonksiyonu Anketi ve İnme Etki Ölçeği 3.0'ı değerleri eğitim öncesi ile karşılaştırıldığında, hem ABILHAND İnme El Fonksiyonu Anketi değerleri hem de İnme Etki Ölçeği 3.0'ın tüm alt boyutlarında istatistiksel olarak anlamlı gelişme olduğu saptandı ($p<0,05$) (Tablo 2).

Tablo 1. Hastaların demografik ve klinik özellikleri

	En az- En çok	Ort±SS veya N (%)
Cinsiyet		
Kadın		28 (57.2)
Erkek		21 (42.8)
Yaş (yıl)	38-69	51.6±11.1
Boy (cm)	157-182	166.5±7.5
Kilo (kg)	56-93	73.8±11.3
BKİ (kg/m2)	19.25-36.68	26.1±4.4
Eğitim durumu		
Okur-yazar değil		3 (6.1)
İlkokul		21 (42.9)
Ortaokul		12 (24.5)
Lise		9 (18.4)
Üniversite		4 (8.1)
Etkilenen taraf		
Sağ		21 (42.8)
Sol		28 (57.2)
İnmenin etiyolojisi		
İskemik		35 (71.5)
Hemorajik		14 (28.5)
Hastalık süresi (yıl)	2-6	2.8±1.5

BKI: Beden Kitle İndeksi, Ort: Ortalama, SS; Standart sapma.

Tablo 2. Hastaların tedavi öncesi ve sonrası ABILHAND İnme El Fonksiyonu Anketi ve İnme Etki Ölçeği 3.0 sonuçlarının karşılaştırılması

	Tedavi Öncesi Ort ± SS	Tedavi Sonrası Ort ± SS	*p
ABILHAND İnme El Fonksiyonu Anketi (0-46)	15.1±5.3	27.2±5.8	***0.0001***
İnme Etki Ölçeği 3.0			
Kuvvet (4-20)	12.7±4.5	18.3±5.1	***0.001***
Hafıza (7-35)	29.9±5.6	31.4±5.2	***0.045***
Duygu (9-45)	26.1±2.2	29.4±3.5	***0.023***
İletişim (7-35)	29.5±3.5	33.4±5.1	***0.011***
Günlük Yaşam Aktivitesi (10-50)	23.9±8.5	37.1±9.7	***0.0001***
Mobilite (9-45)	24.1±8.2	29.6±7.4	***0.018***
El Fonksiyonu (5-25)	9.8±3.9	17.2±3.3	***0.0001***
Sosyal Katılım (8-40)	19.3±3.6	23.1±3.9	***0.025***
İyileşme (0-100)	51.8±13.3	69.3±15.1	***0.001***
Total skor (59-295)	174.4±33.6	208.9±38.8	***0.001***

Ort: Ortalama,SS: Standart sapma
** Bağımlı Gruplar t-Testi*

4. Tartışma ve Sonuç

İnmeli hastalarda etkilenen beyin bölgelerinde nöroplastisitesinin yoğun, bol tekrarlı, duysal ve motor uyaranların kullanıldığı, görev odaklı motor ve fonksiyonel becerilere yönelik uygulamaların önemi bilinmektedir (11,12). Kişiye uygun motor öğrenmenin sağlanmasında kullanılan uyaranların ve geri bildirimlerin yoğunluğunun, günümüzde geliştirilmiş çeşitli teknolojilerin kullanılması ile tutarlı ve etkin bir biçimde ayarlanması mümkündür. Nörolojik hastalıklarda robotik cihazlar kinematik ölçümler ve rehabilitasyon amaçlı uygulamalar hastalarda motor iyileşmeyi kolaylaştırmak için ideal bir araç haline getiren güvenilir, kontrol edilebilir, tekrarlanabilir ve esnek bir şekilde ekstremiteleri aktif veya asistif hareketini uyarmaya olanak sağlamaktadır (12,14,27,32). Üst ekstremite rehabilitasyonunda en sık kullanılan ArmeoSpring cihazın, geniş bir 3 boyutlu çalışma alanında ayarlanabilir kol ağırlığı desteği için yay mekanizmasına sahip pasif aletli bir kol ortezidir ve yardımcı yazılımı Armeo control ile gerçek zamanlı bir cihazı olarak kullanılabilir (28,30,31). Çalışmamızda altı haftalık geleneksel rehabilitasyona ek olarak ArmeoSpring üst ekstremite robotik cihazı ile uygulanan eğitim sonrasında hastaların el fonksiyonu ve yaşam kalitesinde önemli gelişmeler olduğu görüldü.

İnme sonrası rehabilitasyonun temel amacı, hastalığın fonksiyon kaybı üzerindeki etkisini azaltmak ve yaşam kalitesini iyileştirmek amacıyla hareket etmeyi öğrenmeyi teşvik etmektir. Bu nedenle, motor kontrol ve öğrenme süreçlerinde yer alan sinir yapılarını geliştirmek için fonksiyonel görevlerin tekrarlayan, yoğun ve rastgele uygulanmasının gerekli olabileceğini ileri sürmektedir (32). İnme sonrası el fonksiyonlarının yeniden kazandırılması, hastanın fonksiyonelliğinin sağlanması açısından oldukça önemlidir. Bu nedenle tedavide başarıyı arttırmak ve hastayı rehabilitasyon sürecine daha fazla dahil edebilmek amacıyla yeni tedavi yöntemlerinin geliştirilmesi önem kazanmaktadır. İnmeli hastalarda robot destekli eğitim veren çalışmalar incelendiğinde, Kwakkel ve ark. (33) ve Prange ve ark. (34) çalışmalarında robot destekli üst ekstremite eğitiminin subakut ve kronik hastalarda paretik omuz ve dirsek ekleminin kısa ve uzun dönem motor kontrolünü iyileştirdiğini ancak fonksiyonel beceriler üzerinde tutarlı bir etkisi olmadığını ileri sürmüştür. Liao ve ark. (35), robot destekli üst ekstremite eğitiminin ile doz uyumlu aktif kontrol grubunu karşılaştırdıkları çalışmalarında, tüm hastalar 4 hafta boyunca haftada 5 gün, her gün 90-105 dakika süreyle eğitime alınmış. Fonksiyonel görev eğitimi ile birleştirilen simetrik ve iki taraflı robot destekli üst ekstremite eğitimi hastalarda motor fonksiyon, kol aktivitesi ve kendi kendine algılanan bilateral üst ekstremite becerilerinde önemli ölçüde iyileşme olduğunu bildirmişlerdir. Çalışma sonuçlarımıza benzer olarak ABILHAND İnme El Fonksiyonu Anketi sonuçları robot destekli üst ekstremite eğitimine katılan grupta önemli ölçüde daha fazla geliştiği rapor edilmiştir. Bir diğer çalışmada Taveggia ve ark. (17), 54 inmeli hasta üzerinde yaptıkları çalışmalarında müdahale grubu geleneksel rehabilitasyon programına ek olarak ArmeoSpring cihazı ile üst ekstremite eğitimine katılırken, kontrol grubuna ise geleneksel rehabilitasyon programına ek olarak pasif üst ekstremite mobilizasyonu uygulanmıştır. Her iki grupta günde 60 dakika, haftada 5 gün, 6 hafta boyunca eğitim almışlardır. İnme sonrası üst ekstremitede ağrı, disabilite ve spastisitenin tedavisinde robot destekli üst ekstremite eğitiminin etkili olduğunu rapor etmişlerdir. Chan ve ark. (36), çalışmalarında hafif, orta ve şiddetli üst ekstremite etkilenimi olan subakut 48 inmeli hastaya geleneksel rehabilitasyona ek olarak, günde 45 dakika, haftada 5 gün, 3 hafta süreyle ArmeoSpring ile üst ekstremite eğitimine dahil etmişlerdir. Yazarlar, robot destekli üst ekstremite eğitimin, özellikle omuz fleksiyonu gibi dikey kontrolü iyileştirmek için orta ila şiddetli üst ekstremite etkilenimi olan subakut inmeli hastalar için yararlı bir uygulama olduğu ve üst ekstremite kas tonusunda herhangi bir yan etkiye neden

olmadığını bildirmişlerdir. Çalışmamızdan elde edilen sonuçlar da literatürle uyumlu olarak geleneksel rehabilitasyon programına ek olarak uygulanan robot destekli üst ekstremite eğitiminin inmeli hastalarda üst ekstremite fonksiyonlarında daha fazla gelişmeye katkı sağladığı görüşünü desteklemektedir. Çalışmalarda robot destekli üst ekstremite eğitiminin seans sayısı ve süresi farklılık göstermesine rağmen genellikle geleneksel rehabilitasyona ek olarak uygulandığı görülmektedir. Bu da bu eğitimin tek başına uygulanabilir bir eğitim şekli olmadığı diğer tedavilere ek olarak uygulanabilecek alternatif bir yaklaşım olduğunu göstermektedir. Sıklıkla robot destekli eğitimin diğer etkili rehabilitasyon yöntemleriyle kombine edilerek tedavinin etkilerinin artırılmasını önerilmektedir (37).

Üst ekstremite etkilenimi, inme sonrası en sık görülen ve kalıcı bozukluklardan biridir. Üst ekstremitede motor kontrolün kaybı sıklıkla günlük yaşam aktivitelerini ve yaşam kalitesini olumsuz yönde etkilemektedir. İnme sonrası elin fonksiyonel iyileşmesini sağlamak özellikle de ince motor becerilerini kazandırmak çok zordur. Günümüzde mevcut kanıtlar, robot destekli eğitimin inmeli hastalarda üst ekstremite motor kontrolü ve günlük yaşam aktivitesi performansına fayda sağladığını belirtirken (38), yaşam kalitesi üzerine etkisi konusunda kanıtı yetersizdir (39). Hastaların üst ekstremiteleri tamamen iyileşmiş olsa da el becerilerinde uyumlu bir iyileşme olmadığı sürece yaşam kalitesinde anlamlı bir gelişme sağlanamayacaktır. Son yıllarda sıklıkla inmeli hastalarının sağlıkla ilişkili yaşam kalitesi araştırılmaya başlanmıştır. Bu nedenle inme hastalarının yaşam kalitesi değerlendirmesi fiziksel (motor yetersizlik, spastisite, ataksi, ağrı, uyku bozuklukları, yorgunluk vb.) ve sosyal (iş, sosyal iletişim) boyutlarını içermesi gerekir (40). El fonksiyonları, İnme Etki Ölçeği 3.0'ın alt grupları arasında en çok etkilenen alt gruptur. Geçirilmiş inme sonrası tedavi almadan hastaların %85'inde üst ekstremitede fonksiynel yetersizlikler görülürken, ilerleyen aylarda bu oran %55-75'e doğru gerilemekte, %23-43'ünde yetersiz fonksiyonel iyileşme ve yalnızca %5 hastada tam düzelme görülmektedir (40, 41). İnme sonrası dönemde yaşam kalitesini etkileyen faktörleri araştıran çalışmaların sonuçları ile uyumlu olarak İnme Etki Ölçeği 3.0 için hastaların yaşam kalitelerinin motor gelişim ve fonksiyonellik düzeyi arttıkça olumlu yönde gelişme gösterdiği belirtilmiştir (42). Literatürde robot destekli üst ekstremite eğitiminin inmeli hastaların yaşam kalitesi üerine etkisini araştıran çalışma sayısı oldukça kısıtlıdır (11, 43-45). Wu ve ark.(43), 42 inmeli hastaya fizyoterapist temelli, robot destekli eğitim temelli ve kontrol olmak üzer günde 90-105 dakika, haftada 5 gün 4 hafta boyunca bilateral üst ekstremite eğitimi verdikleri çalışma sonuçlarına göre kontrol ile karşılaştırıldığında fizyoterapist ve robot temelli eğitimlerin değerlendirme sonuç ölçütleri üzerinde farklı etkiler gösterdiğini bildirmişlerdir. Fizyoterapist temelli bilateral üst ekstremite eğitiminin distal üst ekstremitenin zamansal etkinliğini, düzgünlüğünü, gövde kontrolünü ve motor bozukluğunu iyileştirdiği, robot destekli eğitimin ise inmeli hastaların omuz fleksiyonunu ve yaşam kalitesini iyileştirdiğini rapor etmişlerdir. Yazarlara göre robot destekli üst ekstremite eğitimin aktif normal eklem hareket açıklığını arttırarak ve muhtemelen el bileği ve önkol spastisitesini azaltarak günlük yaşamda iyileştirilmiş fiziksel koşulların (algılanan kas gücü ve eklem hareket açıklığında artış vb.) yaşam kalitesinin fiziksel işlev alanının ve genel yaşam kalitesinin daha iyi algılanmasına yol açabileceğinden kaynaklandığını ileri sürmektedirler. Bir diğer çalışmada Lee ve ark. (11) 39 kronik inmeli hastayı NMES veya sham stimülasyon ile kombine robot destekli üst ekstremite eğitimi gruplarına ayırdığı çalışmalarında, katılımcılara 4 hafta boyunca günde 90-100 dakika ve haftada 5 gün eğitime dahil etmişler. Robot destekli eğitimle kombine olarak uygulanan sham grubu ile karşılaştırıldığında, NMES grubunda bilek fleksörlerinin modifiye Ashworth ölçeği skorunda, Wolf Motor Fonksiyon Testi hareket kalitesinde ve İnme Etki Ölçeği 3.0'ün el fonksiyonu alanında daha fazla gelişme olduğunu bildirmişlerdir. Yazarlar hastaların yaşam kalitelerindeki artışın el bileği fleksörlerinin spastisitesindeki azalmadan ve paretik eli kullanmadaki başarının öz-yeterliliği artırmasındaki

motivasyondan kaynaklanarak el fonksiyonlarındaki iyileşmeden kaynaklandığını ileri sürmüşlerdir. Zengin Metli ve ark. (45), subakut inmeli hastalar üzerinde yaptıkları çalışmalarında bir gruba geleneksel rehabilitasyona ek olarak günde 30 dakika haftada 5 gün 3 hafta robot destekli üst ekstremite eğitimi verirken kontrol grubuna ise aynı süre boyunca geleneksel rehabilitasyon uygulanmıştır. Kontrol grubuyla karşılaştırıldığında robot destekli eğitim alan bireylerde SF-36'nın fiziksel alt boyutunda anlamlı gelişme görülürken, mental alt boyutunda ise kontrol grubunda daha iyi sonuçlar elde edildiği görülmüştür. Yazarlar geleneksel rehabilitasyon programına ek olarak uygulanan robot destekli üst ekstremite eğitimin, subakut inmeli hastalarda motor iyileşmeyi ve yaşam kalitesini iyileştirmede etkili olduğunu bildirmişlerdir. Çalışmamızda da literatürdeki çalışmalara benzer olarak geleneksel tedaviye ek olarak uygulanan robot destekli üst ekstremite eğitiminin yaşam kalitesinde önemli gelişmelere katkı sağladığı görülmüştür. Çalışmamızda inmeli hastaların yaşam kalitesini değerlendirmek için kullanılan İnme Etki Ölçeği 3.0'ın özelikle el fonksiyonu ve günlük yaşam aktiviteleri alt boyutları önemli gelişmelerin yanı sıra tüm alt boyutlarında anlamlı gelişmeler olduğu görülmektedir. Çalışmamızda inmeli hastaların üst ekstremite motor gelişimlerini ve spastisite durumları değerlendirilmediğinden el fonksiyonlarındaki gelişmelerin uygulanan eğitim programının günlük yaşam aktivitelerine benzer aktivitelerden seçilmiş olmasından ve paretik eli kullanma motivasyonundan kaynaklandığını düşünmekteyiz.

Çalışmanın bazı kısıtlılıkları mevcuttur. Birinci kısıtlılık, tüm hastalarda başlangıç değerlendirme parametrelerine göre anlamlı iyileşme görülmesine rağmen, çalışmanın kontrol grubunun olmamasıdır. İkincisi, retrospektif olarak planlanmış olması ve çalışmaya iyi fonksiyonlu üst ekstremiteye sahip (Modifiye Ashworth Skalası'na göre ≤2) inme hastalarının dahil edilmesidir. Tüm bunlara bağlı olarak, mevcut çalışmanın sonuçları tüm inme hastalarına genellemeye olanak sağlamamaktadır.

Geleneksel rehabilitasyon programı ile kombine edilmiş robot destekli üst ekstremite eğitiminin inmeli hastaların el fonksiyonlarını ve özellikle günlük yaşam aktivitelere katılımlarını önemli ölçüde artırarak yaşam kalitelerini iyileştirdiği görüldü. Robot destekli üst ekstremite eğitimi, katılımcıların etkilenmiş olan üst ekstremitelerini günlük yaşam aktivitelerini iyileştirmede daha fazla kullanmaya motive etmeye katkıda bulunmaktadır. Bu eğitim yönteminin inme sonrası hastaların üst ekstremite rehabilitasyonunda etkili ve eğlenceli ek bir tedavi yöntemi olarak kullanılabileceği düşüncesindeyiz. Literatürde robot destekli üst ekstremite eğitim protokollerinin farklılık gösterdiği görülmektedir, gelecekteki çalışmaların bu eğitim protokolünün optimum yoğunluğunun belirlemesine yönelik olması önem arz etmektedir.

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Research Article / Araştırma Makalesi

Adli Nitelikli Göz Yaralanmalarının Değerlendirilmesi

Evaluation of Ocular Trauma in Forensic Medicine

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Özet

Göz travmaları adli travmatolojide sıkça karşımıza çıkan olgulardır. Göz travmaları kişi ve kurumlar üzerinde yaratacağı sosyal, ekonomik ve psikolojik yük açısındann önem arz etmektedir. Devam edebilecek hukuki sürece esas oluşturacak adli rapoların nesnel verilerle düzenlenmesi, hak kayıplarının önüne geçecek önemli bir faktördür. Çalışmamızda Eskişehir Osmangazi Üniversitesi Hastanesi Adli Tıp Anabilim Dalımıza başvuran adli nitelikli göz travma olgularını incelemek ve literatürle paylaşmak amaçlanmıştır. 2017-2019 yılları arasındaki 3 yıllık dönemde Eskişehir Osmangazi Üniversitesi Hastanesi Adli Tıp Anabilim Dalımıza başvuran adli nitelikli göz travmaları retrospektif olarak değerlendirildi. Olgular yaş grupları, cinsiyet, olayın oluş şekli, yaralanmanın niteliği, yarattığı komplikasyon, yaşamsal tehlike ve işlev zayıflaması veya yitimi yaratıp yaratmadığı yönleriyle değerlendirildi. Veriler SPSS paket istatistik programı aracılığıyla değerlendirildi, ki-kare, pearson ki-kare ve yüzde analizleri yapıldı. Göz yaralanması olan olguların en küçüğünün 2, en büyüğünün 79 yaşında olduğu, yaş ortalamalarının 34.21±1.47 olduğu görüldü. Erkek olguların %79.7 si etkili eylem sonucu adli nitelikli göz yaralanması yaşarken, kadınlar da bu oran %75 olarak bulundu. Olguların 15 inde işlev zayıflaması/yitimi olduğu belirlendi. Yaralanma türü ile işlev zayıflaması/yitimi arasında anlamlı bir farklılık olduğu görüldü. Penetran yaralanmaların %54.5 inde işlev zayıflaması ya da yitimi olduğu, künt yaralanmalarda ise bu oranın %4.8 olduğu görüldü. Adli nitelikli göz yaralanmaları sebep olduğu tedavi ve bakıcı masrafları, engellilik hali, psikolojik yük dolayısıyla kişi ve kurumlar için önemlidir. Devam edebilecek hukuki sürece esas oluşturacak adli raporların nesnel ve nitelikli olması için ve kişinin hak kayıplarının önüne geçebilmek adına, göz yaralanmaları göz hastalıkları uzmanları ile adli tıp uzmanlarının multidispliner değerlendirmesi gereken önemli bir adli travmatoloji konusudur.

Anahtar Kelimeler: Göz yaralanması, adli göz travmaları, adli tıp

Abstract

Ocular traumas are common cases in forensic traumatology practice. Ocular trauma is important in terms of social, economic and psychological burden. Forensic reports with objective data that will form the basis of the legal process that can continue is an important factor to prevent loss of rights. This study aims at reviewing the epidemiology of ocular trauma presenting to Eskisehir Osmangazi University Hospital. This is a retrospective epidemiological study of patients admitted to Eskisehir Osmangazi University Hospital with ocular trauma from 2017 till 2019. Cases were analyzed with respect to age, sex, the way the incident occurred, the complications it caused. And it was evaluated in terms of whether it was life-threatening and whether it caused visual acuity impairment or loss. Spss software was applied to produce the chi-square, pearson chi-square and percentage analyses. Values of $p<0.05$ were assumed to be statistically significant. The age of cases ranged between 2-79 and their mean age was 34.21±1.47. It was determined that 15 of the cases had impairment/loss of function. There was a significant difference between the type of injury and the impairment/loss of function. 54.5% of penetrating injuries had functional impairment or loss, while this rate was 4.8% in blunt injuries. Traumatic ocular injuries are an important issue of forensic traumatology that must be evaluated by ophthalmologists and forensic medicine specialists together in order to prepare objective and qualified forensic reports that will form the basis of the legal process that can continue and to prevent loss of rights.

Keywords: Ocular injuries, judicial ocular injuries, forensic medicine

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1. Giriş

Göz yaralanmaları, göz acilleri içinde önemli bir yer tutmakla birlikte aynı zamanda adli tıp açısından da önem arz eder. Hem ceza hem de tazminat hukuku açısından, düzenlenen adli raporlarda, yaralanmanın ağırlık derecesi ile kalıcı nitelikte tam ya da kısmi özür durumunun aydınlatılması gerekir. Çalışmalarda tüm vücut yaralanmalarının %7'sini, tüm göz hastalıklarının %10-15'ini göz travmalarının oluşturduğu belirtilmektedir (1,2). Gözler tüm vücut yüzey alanın % 0,27'sini, yüz bölgesinin % 4'ünü kaplar buna rağmen travmadan en çok etkilenen organlardan birisidir (3). Göz travmaları özellikle gelişmekte olan ülkelerde tek taraflı görme kayıplarının önemli nedenlerinden biridir (1). Epidemiyolojik bir çalışmada, her yıl yaklaşık 55 milyon göz yaralanması olduğunu belirterek oküler travma sıklığına dikkat çekilmiştir (4).

Görme kaybı sağlık sorunu olmasının yanında sosyal bir engeldir ve yaratacağı tedavi masrafları, bakıcı masrafları, iş gücü kaybı, ruhsal bozukluklar açısından da önemlidir. Araştırmalara göre, ortopedik engel sonrası en çok görülen özür durumunun görme engeli olduğu bildirilmiştir. Görme engelinin % 25.45 oranla kaza sonrası oluştuğu belirtilmektedir (5).

Adli göz yaralanmalarında devam edebilecek hukuki süreç için adli raporlar önem arz etmektedir. Eşlik edebilecek orbita tavan kırığı ve kafatası kırıklarının, kafa içi kanama, kontüzyon ve laserasyonunun yaşamsal tehlike oluşturacağı bilinmelidir. Göz kapağı ve çevresinde ekimoz, hematom, yüzeyel laserasyonların, konjonktivada subkonjonktival kanama, korneada perforasyona yol açmayan abrazyon ve kontüzyon gibi basit lezyonların basit tıbbi müdahale ile giderilebilecek nitelikte haller olduğu bilinmelidir. Hukuk sistemimizde duyu veya organlardan birinde sürekli işlev zayıflaması veya yitimi halleri, neticesi sebebiyle ağırlaşmış yaralama durumunu oluşturmaktadır. İşlev yitimi veya zayıflaması yönüyle değerlendirme yapılırken her gözün ayrı bir duyu organı olarak değerlendirilmesi gerekmektedir (6).

Bu çalışmada Eskişehir Osmangazi Üniversitesi Hastanesi Adli Tıp Anabilim Dalı'na başvuran adli nitelikli göz travma olgularının incelenmesi verilerin literatürle paylaşılması amaçlanmıştır.

2. Gereç ve Yöntem

Bu çalışmada 2017-2019 yılları arasında (3 yıl) Eskişehir Osmangazi Üniversitesi Hastanesi Adli Tıp Anabilim Dalımıza başvuran adli nitelikli göz travmaları retrospektif olarak değerlendirildi.

Olgular yaş grupları, cinsiyet, olayın oluş şekli, yaralanmanın niteliği, yarattığı komplikasyon, yaşamsal tehlike ve işlev zayıflaması veya yitimi yaratıp yaratmadığı yönleriyle değerlendirildi. Olguların adli tıbbi değerlendirilmesinde, "*Türk Ceza Kanunu'nda tanımlanan yaralama suçlarının adli tıp açısından değerlendirilmesi*" kılavuzundan yararlanılmıştır. Veriler SPSS paket istatistik programı aracılığıyla değerlendirildi, ki-kare, pearson ki-kare ve yüzde analizleri yapıldı. $p<0.05$ istatistiksel olarak anlamlı kabul edilmiştir.

Çalışma, Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Girişimsel Olamayan Klinik Araştırmalar Etik Kurulunun 14.08.2020 tarihli ve 2020-266 sayılı onayı ile yapılmıştır.

3. Bulgular

Çalışmanın kapsadığı 3 yıllık dönemde göz yaralanması olan 198 olgu olduğu tespit edildi. 3 yıllık dönemdeki adli travmatolojiyi ilgilendiren 6407 olgudan % 3,1 kadarında göz yaralanması olduğu tespit edildi.

Göz yaralanması olan olguların en küçüğünün 2, en büyüğünün 79 yaşında olduğu, yaş ortalamalarının 34.21±1.47 olduğu, olguların en sık 30 ila 39 yaş grubu arasında olduğu (%29.3) belirlendi. Olguların %79.8'inin (n=158) erkek, %20.2'sinin (n=40) kadın olduğu belirlendi.

Cinsiyet ve yaş grubunun dağılımı tablo 1 de sunulmuştur. Yaş grubu ile cinsiyet arasında anlamlı bir ilişki saptanmamıştır. Her iki

cinsiyette olguların önemli bir kısmı 20 ila 40 yaş arasında toplanmıştır. (p>0.05) (Tablo 1).

Tablo 1. Olguların yaş gruplarının, cinsiyete göre dağılımı

Yaş Grubu	Cinsiyet				Toplam	
	Erkek		Kadın			
	n	%	n	%	n	%
0-18	19	12,0	3	7,5	22	11,1
19-29	46	29,1	9	22,5	55	27,8
30-39	45	28,5	13	32,5	58	29,3
40-49	20	12,7	11	27,5	31	15,6
50 ve üzeri	28	17,7	4	10,0	32	16,2
Toplam	158	100,0	40	100,0	198	100,0

χ^2=6,935 P>0,05

Olguların 156'sının (% 78,8) etkili eylem sonucu yaralandığı belirlendi. Olay türleri ile cinsiyet arasında anlamlı bir farklılık olmadığı görüldü (Tablo 2, P>0,05). Erkek olguların % 79,7'sinin (n=126), kadın olguların % 75'inin (n=30) etkili eylem sonucu yaralandığı belirlendi.

Tablo 2. Cinsiyetin olay türlerine göre dağılımı

	Cinsiyet				Toplam	
	Erkek		Kadın			
Olay türü	n	%	n	%	n	%
Etkili Eylem	126	79,7	30	75,0	156	78,8
Kaza	32	20,3	10	25,0	42	21,2
Toplam	158	100,0	40	100,0	198	100,0

χ^2=0,430 P>0,05

Olgularımızın 187 sinin künt, 11 inin penetran yaralanma şekilde olduğu, yaralanma şekli ile cinsiyet arasında anlamlı bir ilişki olmadığı belirlendi (p>0.05). Olguların 15'inde işlev zayıflaması/yitimi olduğu belirlendi. Yaralanma türü ile işlev zayıflaması/yitimi arasında anlamlı bir farklılık olduğu görüldü (p<0.01). Penetran yaralanmaların %54.5 inde işlev zayıflaması ya da yitimi olduğu, künt yaralanmalarda ise bu oranın %4.8 olduğu görüldü (Tablo 3).

Tablo 3. Olayın oluş şeklinin ile işlev zayıflığı/yitimi durumuna göre dağılımı

İşlev yitimi veya zayıflaması	Olayın oluş şekli				Toplam	
	Künt		Penetran			
	n	%	n	%	n	%
İşlev Yitimi veya Zayıflaması Yok	178	95,2	5	45,5	183	92,4
İşlev Yitimi veya Zayıflaması Var	9	4,8	6	54,5	15	7,6
Toplam	187	100,0	11	100,0	198	100,0

Pearson χ^2=36.698 Pearson ki-kare (P<0.0001)

Olguların 98 (%49.5)'inin basit tıbbi müdahale ile giderilebilir nitelikte olduğu, 100 (%50.5)'ünün ise basit tıbbi müdahale ile giderilebilir nitelikte olmadığı şeklinde raporlandığı görüldü.

Göz yaralanması olan 198 olgunun 24'ünde (%12.1) eşlik eden lezyonların yaşamsal tehlikeye neden olduğu belirlendi.

4. Tartışma

Adli travmatolojiyi ilgilendiren yaralanmalarda, olguların çoğunlukla erkek ve genç yaş grubunda oldukları bildirilmiştir (7-12). Ankara Üniversitesi Tıp Fakültesi Adli Tıp Anabilim Dalı'na 7 yıllık dönemde başvuran 1053 olgunun 680'inin (% 65,5) erkek olduğu, olguların en sık 21-30 yaş grubunda olduğu bildirilmiştir (10). Göz travmaları ile ilgili yapılan epidemiyolojik çalışmalarda da göz travmalarının genellikle erkeleri ilgilendirdiği bildirilmiştir (13-19). Van'da yapılan, göz travmalarının değerlendirildiği bir çalışmada, göz travmasına maruz kalan olguların % 81,6'sının erkek olduğu ve yaş ortalamasının 18,7 olduğu bildirilmiştir (19). İstanbul'da yapılan çalışmada olguların % 86,5'inin erkek olduğu, yaş ortalamasının 27,8 olduğu bildirilmiştir (16). Manisa'da acil servise başvuran göz travmalarının değerlendirildiği bir çalışmada olguların % 74,7'sinin erkek olduğu, olguların en sık (% 28,6) 30-39 yaş grubunda olduğu bildirilmiştir (20). Sunulan çalışmada, Olguların %79.8'inin (n=158) erkek, %20.2'sinin (n=40) kadın olduğu, olguların en sık 30-39 yaş grubunda olduğu ve yaş ortalamasının 34,2 olduğu belirlenmiştir. Travmatik göz yaralanmalarının daha sık genç erkeklerde görülmesi bu kişilerin; daha sık trafikte olmaları, kaza olasılığı yüksek riskli işlerde daha sık olarak çalışmaları, daha sosyal olmaları, dışarıda daha fazla vakit geçirmeleri ve daha sık kavgaya karışmaları ile açıklanabilir.

Olgular, olay türüne göre değerlendirildiğinde, 156 olgunun (% 78,8) etkili eylem sonucu yaralandığı belirlendi. Bu oran Çakırer ve arkadaşlarının yaptığı çalışmada %8,7 olarak bildirilmiştir (16). Göz kliniklerinde yapılan çalışmalarda, göz travmalarının daha sık olarak düşme, çarpma gibi küçük kazalar olarak bildirilmiştir (16,17,21). Sunulan çalışmada darp sonucu göz yaralanma oranının yüksek çıkması, çalışmanın bir göz kliniğin değil, adli tıp biriminde yapılmış olmasına bağlanmıştır. Darp nedeniyle yaralanan olguların fazla olasının da etkisi ile olguların % 94,4'ünün (n=187) künt travma şeklide olmasına neden olmuştur. Göz kliniklerine travma nedeniyle gelen tüm olgular adli vaka olmayabilir. Ancak göz hekimleri de, diğer tüm hekimler ve sağlık çalışanları gibi, suç ile karşılaştıklarında bunu bildirmek ile yükümlüdürler. Göz travması olan olgular, adli olgu açısından değerlendirilmeli, adli vaka oldukları anlaşılırsa ve daha önce bildirimi yapılmamışsa ilgili kolluk kuvvetlerine gerekli bildirim yapılmalıdır (22). Olay türü ile cinsiyet arasında anlamlı bir farklılık bulunmadığı belirlenmiştir (Tablo 2, P>0,05). Olguların çoğunluğu erkek olmakla birlikte (% 78,8) olay türleri arasında farklılık bulunmaması, kadına yönelik şiddet olgularının artması ile açıklanabilir.

Adli raporlarda aydınlatılması gereken konulardan birisi de yaralanmanın işlev zayıflığı/yitimi niteliğinde olup olmadığıdır (6,23). Sunulan çalışmada, olguların 15'inde (% 7,6) işlev zayıflığı/yitimi saptanmıştır. Yaralanma şekli ile, işlev zayıflığı/yitimi arasında anlamlı bir ilişki olduğu belirlenmiştir (Tablo 3, P<0.0001). Penetran yaralanmaların %54.5 inde işlev zayıflaması ya da yitimi olduğu, künt yaralanmalarda ise bu oranın %4.8 olduğu saptanmıştır. Yapılan çalışmalarda, penetran yaralanmaların, gözde daha derin dokular etkilediği ve işlevseliği daha fazla etkileyecek yaralanmalara neden olduğu bildirilmiştir (24-26). Tüm travmatik göz yaralanmalarında, yaralanma sonrası, göz fonksiyon kayıpları göz hastalıkları uzmanınca değerlendirilerek adli raporlara kaydedilmelidir. Gerekirse tekrarlı muayeneler yapılmalıdır.

Travmatik göz yaralanmaları neden olacağı, fonksiyon kayıpları, oluşturacağı tedavi masrafları, bakıcı giderleri, ruhsal bozukluklar, sürekli özür halleri yönüyle önemlidir. İş kazası, etkili eylem, trafik kazası gibi durumlarda devam edebilecek ceza davaları ve tazminat davaları için esas teşkil edecek adli raporların objektif ve nesnel değerlendirilmiş olması önem taşımaktadır. Göz travmalarının hem akut hem de uzun dönemde oluşablecek komplikasyonları açısından da göz hastalıkları uzmanlarından görüş alınması önemlidir. Göz travmaları tek başlarına yaşamsal tehlike oluşturmazlar.

Ancak mevcut olabilecek diğer sistem yaralanmaları için de ilgili branşlarla multidisipliner yaklaşım benimsenmelidir.

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Research Article / Araştırma Makalesi

Administration of Attenuated Live Vaccines Before and After Liver Transplantation in Childhood: Single Center Experience in Turkey

Çocukluk Yaş Grubunda Karaciğer Nakli Öncesi ve Sonrası Zayıflatılmış Canlı Aşı Uygulamaları-Türkiye'den Tek Merkez Deneyimi

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Abstract

The aim of this study was to evaluate the attenuated live vaccine administration before and after liver transplantation. This study was carried out at the Child Health Surveillance Unit of the Social Pediatrics Department. Besides healthy children, children with special needs are being followed-up at the Unit. Each child has a personal health record in the unit. The health records of patients who had received attenuated live vaccine before liver transplantation under 1 year of age or after liver transplantation were evaluated. Demographic characteristics, data showing immunologic status before vaccination, vaccine related reactions and serologic responses were obtained from health records of each child. Retrospective files of 5 patients who were in follow-up were examined. Four patients at least 2 years after the liver transplantation had attenuated live vaccination (measles-mumps-rubella vaccine and / or chickenpox vaccine). No adverse reaction was noted after the immunization among these 4 children. A 6-month-15-day-old infant who was a candidate for liver transplantation had been vaccinated with measles-mumps-rubella and chickenpox vaccine and it was determined that the serological response after vaccination was not complete in the baby who did not have any adverse reactions after vaccination. Our findings demonstrated that despite the use of immusuppressive therapy, it is safe to apply attenuated live vaccines after the transplantation if appropriate conditions were provided. The timing of the rapid effective immunization before transplantation under one year of age needs to be further investigated.

Keywords: Child, liver transplantation, attenuated live vaccination

Özet

Karaciğer nakli öncesi ve sonrası çocuklarda canlı aşı uygulamalarının değerlendirilmesidir. Çalışmamız Sosyal Pediatri Bilim Dalı Çocuk Sağlığı İzlem Birimi'nde yapılmıştır. Birimde sağlıklı çocukların yanı sıra özel ihtiyaçları olan çocuklar da takip edilmektedir. Birimde takipli her çocuğun sağlık kaydı bulunmaktadır. 1 yaşın altında karaciğer nakli öncesinde veya karaciğer nakli sonrasında zayıflatılmış canlı aşı almış hastaların sağlık kayıtları değerlendirildi. Her çocuğun sağlık kayıtlarından demografik özellikler, aşılama öncesi immünolojik durumu gösteren veriler, aşı ile ilgili reaksiyonlar ve serolojik yanıtlar kaydedildi. Takipte olan 5 hastanın geriye dönük dosya incelemendi. Bunlardan dördüne nakilden en erken 2 yıl sonra olmak üzere zayıflatılmış canşı aşı (kızamık-kızamıkçık-kabakulak ve/veya suçiçeği aşıları) uygulanmıştır. Bu dört hastanın hiçbirinde aşı sonrası bir sorun gelişmemiştir. Nakil öncesi zayıflatılmış canlı aşı uygulanan 6 ay 15 günlük bebekte kızamık- kızamıkçık-kabakulak ve suçiçeği aşıları uygulanmıştır. Aşı sonrası herhangi bir istenmeyen reaksiyon gözlenmeyen bebekte aşı sonrası serolojik yanıtın tam olmadığı belirlenmiştir. Bulgularımız nakil sonrası immunsüpresif kullanmakta olan çocuklarda gerekli değerlendirmeler sonrasında zayıflatılmış canlı aşı uygulanmasının güvenli olduğunu ortaya koymaktadır. Diğer yandan karaciğer nakli planlanan, acil aşılanması gereken 1 yaş altındaki hastalarda KKK ve suçiçeği aşı uygulamaları sonrası yeterli yanıt oluşması konusunda ayrıntılı değerlendirme gerekmektedir.

Anahtar Kelimeler: Çocuk, karaciğer nakli, canlı aşılama

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1. Introduction

Generally, inactive vaccine administrations are continued 2-6 months after the transplantation depending on their conditions, and if they have not been vaccinated previously, a new vaccine schedule is established (1). However, there are various approaches for live vaccine administration after solid organ transplantation. This is due to the lifelong use of immunosuppressive drugs (2-5). Recently, the suggestions supporting attenuated live vaccine (ALV) administration after solid organ transplantation have started to take place in the literature (6-11).

It is reported that the patients under 1 year of age can have attenuated live vaccination during the preparation stage of solid organ transplantation (1,3). On the other hand, there are different opinions regarding the optimal timing of vaccination, particularly considering maternal antibodies (12-14).

This article aims to present the results of ALV administration in post-transplant 4 patients and in a pre-transplant infant.

2. Methods

An average of 25 patients are transplanted annually in the İstanbul Faculty of Medicine Department of Pediatrics Division of Pediatric Gastroenterology, a leading center for pediatric liver transplants in Turkey both living organ transplantation and, less frequently, cadaver transplantation are performed in the Liver and Biliary Tract Surgery unit of this center. The transplant preparations of patients who are followed up by the İstanbul Faculty of Medicine Division of Pediatric Gastroenterology and for whom liver transplantation is decided due to chronic liver disease are carried out in cooperation with several medical departments. These patients are also monitored by the İstanbul Faculty of Medicine Department of Pediatric, Division of Social Pediatrics for age-appropriate vaccination. An individual patient file is created for these children, past vaccinations are evaluated, an age- appropriate vaccination scheme is established. A follow up programme is organized for this purpose. Except for particular cases, transplant patients receive methylprednisolone for the first 3 months, and on tacrolimus immunosuppression immediately after the transplant for lifelong period. The patient is followed up by the gastroenterology department and the transplantation unit every month for the first 6 post-transplantation months, and at gradually increasing intervals after that. Immunosuppressive drug levels are regularly controlled, and doses are adjusted accordingly. The tacrolimus dose is generally planned as 8-10 ng/mL in the acute period, 5-10 ng/mL in the subsequent period, and 3-5 ng/mL after the first year, where the dosage is adjusted according to clinical condition (15). After the transplant, the Division of Social Pediatrics establishes a vaccination schedule for the remaining vaccines. If necessary, ALV administrations are included in the schedule after consulting with the Department of Pediatric Immunology.

A personal health record is available for every patient who is followed-up by the Division of Social Pediatrics for vaccination before or after transplantation. A detailed history is taken, and physical examination is performed at each encounter. Any contraindications for ALV after transplantation is evaluated according to the criteria (Table 1) developed by Shinjoh et al (7). Serological condition is evaluated both before and after ALV. The patient's family is informed in detail to obtain consent prior to immunization. Families were informed about vaccine reactions (erythema, swelling, pain, rash and fever) and they were asked to call our unit if any of these reactions occur. After vaccination, patients are closely monitored, and any problems or rejection are evaluated and recorded. All evaluations are made by a multidisciplinary team consisting of the Divisions of Social Pediatrics, Pediatric Immunology, and Pediatric Gastroenterology.

Table 1. Eligibility criteria for the attenuated vaccination after liver transplantation (7)

1. Positive intention of the family for vaccination of the child and the approval of the unit which follows up the patient.
2. ≥ 2 years after liver transplantation
3. Borderline or negative serological value for any measles, mumps, rubella and/or varicella infections
4. Tacrolimus level <5 ng/mL or cyclosporine level <100 ng/mL
5. Not using IVIG, steroid (>0.2 mg/kg/day) or having blood product for the last 6 months
6. Normal serum levels of liver enzymes (AST, ALT) total bilirubin, and no rejection finding within the last 6 months
7. Evaluation of humoral and cellular immunity;
    a. IgG >500 mg/dL
    b. Total lymphocyte count >1000/ µL or children ≥ 6 years of age and >1500/ µL for those younger than 6 years
    c. CD4 >700/ µL for < 6 years of age, and >500/ µL for 6 years old and older
    d. CD4/CD8 >1
    e. Normal proliferation test

In this study, we retrospectively evaluated the patients' files in the Division of Social Pediatrics. The results of measles-mumps-rubella (MMR) and / or chickenpox vaccinations to 4 patients who have underwent liver transplantation more than 2 years ago, and to a patient younger than 1 year of age before transplantation were evaluated. We recorded the reasons for transplantation, the timing of transplantation, vaccination status before the transplantation, the timing of ALV administration after the transplantation, the biochemical results, pre- and post-vaccination serologic responses, any local or systemic reactions, and the follow-up duration. The Enzyme Linked Immunosorbent Assay (ELISA) was used to evaluate serological responses at least 1 month after vaccination.

The İstanbul Faculty of Medicine local ethical committee approved the study (ethics committee decision number: 2020/323).

3. Results

According to the retrospective evaluation of patient files between October 2018 and February 2020 in the Social Pediatrics Outpatient Clinic, ALV administered to 5 patients before or after liver transplantation. The characteristics of our patients are summarized in Table 2.

All patients are still under follow-up by our clinic. The ages of the patients at the time of ALV administration are presented in Table 2. Three patients had living-donor transplantations and 1 had a cadaver transplantation, and at least 2 years had passed form the transplantation to the time of vaccination. All patients were using tacrolimus for immunosuppression, and two consecutive measurements of tacrolimus were <5 ng/mL at the time of vaccination. The patients had not received intravenous Ig (IVIG), steroids, blood products, Rituximab or mikofenolat mofetil (MMF) nor had a history of rejection within the past 6 months. Liver enzyme levels (AST, ALT), total bilirubin, total lymphocyte count (<1500/µL for <6 years old, >1000/µL for >6 years old), lymphocyte subgroups, and lymphocyte proliferation test results were normal and IgG was >500 g/dL.

The case 1 underwent liver transplantation due to Crigler–Najjar syndrome type 1 at one year of age and had received all vaccinations until that time. The patient tested negative for measles IgG and the family wished their child to be vaccinated with measles vaccine, therefore, the patient underwent the examinations presented in Table 1 and assessed for serological condition. Since the patient was measles seronegative, and the conditions were favorable, MMR vaccine was administered because a single measles vaccine was not available at the time of the administration. The patient did not develop a reaction after vaccination. The patient has been followed up for 17 months after vaccination and for 20 months in total.

Table 2. Characteristics and vaccination status of patients

	Case 1*	Case 2*	Case 3*	Case 4*	Case 5**
Gender	F	F	M	M	M
Application age (year)	9 + 5/12	4	9+10/12	9+6/12	3 months
Measles vaccine administration status before transplantation/number of dose	+/1	-	+/1	+/1	-
Rubella vaccine administration status before transplantation/number of dose	+/1	-	+/1	+/1	-
Mumps vaccine administration status before transplantation/number of dose	+/1	-	+/1	+/1	-
Varicella vaccine administration status before transplantation/number of dose	+/1	-	-	-	-
Reason for transplantation	Crigler–Najjar syndrome type 1	Biliary atresia	Fulminant hepatitis	Biliary cirrhosis	Methylmalonic acidemia
Type of liver transplantation	Living donor	Living donor	Cadaver	Living donor	-
Age at transplantation (year-month)	1 year	9 months	4 years	1 year	-
Time passed after transplantation at the time of vaccination (year)	8	3	5	8	NA
Evaluations at the application					
Measles IgG	Negative	Negative	Positive	Negative	NA
Rubella IgG	Positive	Negative	Positive	Positive	NA
Mumps IgG	Positive	Negative	Positive	Negative	NA
Varicella IgG	Positive	Negative	Negative	Positive	NA
AST (U/L)	24	34	35	34	NA
ALT (U/L)	15	22	25	20	NA
Total bilirubin (g/dL)	1.2	0.66	0,26		NA
IgG (mg/dl)	814	1095	1282	1385	NA
Total leukocyte count-absolute lymphocyte count /µL	10.300 -3300	5710-2500	6600-2700	9400-3290	NA
Lymphocyte subgroups					NA
CD4 (%) - CD8 (%)	32 – 25	38 - 23	28 - 21	42 - 18	NA
CD4/CD8	>1	>1	>1	>1	NA
Lymphocyte proliferation test	Normal	Normal	Normal	Normal	NA
Tacrolimus level (2 sequential value) (ng/mL)	4,9 – 4,6	4,3 – 3.9	4 – 3,7	3.1 -3,7	NA
Administered vaccine					
MMR	+	+	-	+	+
Varicella	-	+	+	-	+
Evaluation after vaccine administration					
Measles IgG	Positive	Positive	NA	-	Negative
Rubella IgG	NA	Positive	NA	NA	Negative
Mumups IgG	NA	Negative	NA	-	Positive
Varicella	NA	Negative	Negative	NA	Negative
Local/systemic reactions after vaccination	Not observed	Not observed	Not observed	Not observed	Not observed
Antibody evaluation time after vaccination (month)	3	3	1-2	1,5	5,5
Total duration of follow up time (month)	20	17	16	15,5	15,5
Follow up after vaccination (month)	17	9	4	1,5	12

**: Posttransplant; **:Pretransplant; M:Male; F: Female; NA: Not available; MMR: Measles-Mumps-Rubella*

The case 2 had biliary atresia and underwent a Kasai procedure at 2 months of age and liver transplant at 9 months. The patient had not received MMR or varicella vaccines before the transplant and tested negative for varicella IgG, measles IgG, rubella IgG and mumps IgG. The family wished their child to be vaccinated; therefore, the patient underwent the examinations presented in Table 1 and had favorable results. She received the MMR vaccine immediately, and varicella vaccine one month later. The patient did not develop a reaction after the vaccinations. Three months after vaccination, the patient tested negative for varicella IgG and mumps IgG. It was decided to administer a second dose to the patient before the transplantation. However the consecutive tacrolimus measurements were not favorable, and the patient was put on follow up for appropriate tacrolimus levels. The patient has been followed up for 9 months after vaccination and for 17 months in total.

The case 3 underwent liver transplantation at the age of 4 years due to fulminant hepatitis. The patient tested negative only for varicella IgG and the family wished the patient to be vaccinated. Subsequently the patient underwent the examinations presented in Table 1. The patient had the varicella vaccination. The patient did not develop a reaction after vaccination. The 1-month and 2-month assessments revealed that the patient was seronegative for varicella. The patient has been followed up for 4 months after vaccination and for 16 months in total. A second dose of varicella vaccine was currently planned for the patient who was not immunized against varicella prior to transplantation.

The case 4 underwent liver transplantation at the age of one year due to biliary cirrhosis. The patient tested negative for measles IgG and mumps IgG and underwent the examinations presented in Table 1. The patient received an MMR vaccine and did not develop a reaction after vaccination. The patient was to be assessed for mumps IgG and measles IgG 1.5 months after vaccination; however, parents decided to defer serological assessment. The patient has been followed up for 15 months after vaccination and for 1.5 years in total.

The case 5 is followed up with the diagnosis of methylmalonic acidemia. MMR and varicella vaccines were administered to the patient at the age of 6 months and 15 days for rapid vaccination before transplantation. The patient did not develop a reaction after the vaccinations. The patient was kept on follow-up and had not underwent a transplantation at 12 months of age. The patient was subsequently evaluated to decide for re-vaccination and tested negative for measles IgG, rubella IgG, and varicella IgG. The patient received second doses of MMR and varicella at 12 months of age. The patient did not develop a reaction after the second doses of vaccines. The patient has still not transplanted. The patient has been followed up for 12 months after vaccination and for 15.5 months in total.

4. Discussion

Today, children with chronic diseases are more likely to survive with the available treatment options. This makes it even more important to vaccinate these children. Further studies are needed in this context, particularly regarding live vaccinations. This article presents the experiences of a leading children's liver transplantation center from Turkey regarding ALV administration before and after transplantation. ALV was administered to a total of 5 cases as per certain criteria and none of them developed any vaccine-related issues.

The World Health Organization reported an increasing prevalence of measles in Europe according to 2019 data, with 2666 cases in Turkey (16). The most effective way to prevent measles infections is vaccination. The Expanded Programme for Immunization of Turkey recommends administering the measles, mumps, and rubella vaccine in two doses at 12 months of age and at 6 years, and the varicella vaccine as a single dose at 12 months. As of November 2019, the measles vaccine was added to the program at 9 months

of age (17). Rubella immunization is very important especially for females at reproductive age due to the risk of congenital rubella syndrome (5). Viral infections can be more severe in patients who are on immunosuppressive therapy compared to healthy individuals. For these reasons, immunization is important for vaccine-preventable diseases.

Although ALV administration is generally considered to be contraindicated after solid organ transplantation, it has long been reported that varicella vaccine can be administered after at least 2 years after transplantation and if there is no evidence of rejection or graft-versus-host disease (GVHH). Recent studies started to report that ALV administration is safe for post-transplantation patients (6,7,11).

Shinjoh et al. reported that several criteria should be taken into consideration for ALV administration after solid organ transplantation (7). These criteria included the evaluation of cellular and humoral immunity, and identification of the most favorable conditions where immunosuppression was at the lowest level. We considered these criteria for our transplant patients and administered the vaccines if all criteria were met (Table 1). Shinjoh et al. indicated that blood tacrolimus should be <5ng/dL and at least 2 years must have passed after transplantation before vaccination. Kawano et al. accepted the time of 1 year to pass after transplantation as the criterion for vaccination (8). Another publication recommends waiting for at least 1 year after transplantation and to ensure that two consecutive tacrolimus values are <8 ng/mL and that at least 2 months have passed after rejection findings (11). Since the recommendatory article of Suresh et al. was published after the establishment of vaccination schedules of our patients, our vaccine administrations were carried according to the criteria defined by Shinjoh et al. Together with the criteria included in this assessment, we included having two consecutive measurements of tacrolimus <5ng/mL and not having a history of blood product administration in the last 6 months as additional criteria. Blood product administration has been determined as an additional criterion since it affects the efficacy of the parenteral ALV administration.

Guidelines indicate that MMR and varicella vaccines can be administered at 6-11 months (1,3,18). However, there is no clear consensus on timing. A study by Ganz et al. demonstrated that neutralizing antibody levels were lower in patients where the first dose of measles vaccine was administered at the age of 6 months compared to 9 months and 12 months (13). In a study from our unit Devecioğlu et al. reported the seropositivity rates of mothers for measles, mumps, rubella, and varicella at the first month after birth as 95.7%, 92.8%, 92.8% and 96.7%, respectively. Furthermore, during the first month of life, 88% of children were seropositive for measles, 81.7% for mumps, 89% for rubella, and 96.7% for varicella whereas at six months, this ratio was 25% for measles, 14.6% for mumps, 23.2% for rubella, and 17.1% for varicella (13). Karaayvaz et al. reported the prevalence of measles seropositivity as 72.5% in cord blood, 2.6% at six months, and 3.6% at 9 months (19). Lochlainn et al. stated that a high seropositivity rate was achieved with the administration of the second dose after the first measles-containing vaccine dose which was administered before 9 months of age (20). On the other hand Princi et al. also proposed that antibody response was lower in patients who were vaccinated before 9 months compared those who were vaccinated after 9 months (21). In our study, the antibody levels of Case 5 assessed after 5.5 months indicated that the vaccine had provided partial seroconversion. This may raise the question regarding the earliest and most appropriate time for rapid vaccination under one year of age and the need for maternal antibody determination before vaccination. Nevertheless, each patient should be individually assessed, and it should be considered that a live vaccine can be administered until 4 weeks before transplantation when establishing a vaccination schedule.

Our study reflects data from a single center. The major limitation of the study is the small

number of subjects. However, it offers important data that can be used in this context.

We conclude that ALV administration is possible in patients with liver transplantations at an immunologically appropriate time. It is also important to complete immunization rapidly by a live vaccine at the earliest possible time before transplantation while considering the presence of maternal antibodies. Since our study is the first publication from Turkey reporting the administration of ALV after liver transplantation, we believe our findings will shed light on future administrations performed in other centers.

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Research Article / Araştırma Makalesi

COVID 19 Pandemisi Nedeniyle Evlerinde Sosyal İzolasyon Yaşayan ve Daha Önceden Fibromyalji Sendromu Tanısı Almış Bireylere Uygulanan Tele Rehabilitasyonun Etkinliğinin Araştırılması

Investigation of the Effectiveness of Tele-Rehabilitation in Individuals Experiencing Social Isolation at Home Due to the COVID-19 Pandemic and Previously Diagnosed with Fibromyalgia Syndrome

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Özet

Fibromyalji hastalarındaTele-rehabilitasyon uygulamasının hastalığın semptomları üzerine olan etkisinin araştırılması amaçlanmıştır. Olgular kuvvetlendirme (n=20), germe-gevşeme (n=20) ve kontrol (n=20) olmak üzere üç grup olarak randomize edildi. Çalışma 55 kişi ile sonlandırıldı. Tüm olgularda; Fibromyalji Etki Sorgulama Ölçeği (FIQ), Görsel Analog Skala (VAS), Yaşam Kalitesi Ölçeği (SF-36), Beck Depresyon Envanteri (BDE), Pittsburgh Uyku Kalite İndeksi (PUKİ) ve Pozitif-Negatif Duygu Durumu Ölçeği (PANAS), 5 Defa Otur-Kalk Testi (5-DOKT), Zamanlı Kalk ve Yürü Testi (TUG) ve V-Otur-Uzan Testi (VOUT) kullanıldı. Grupların demografik ve klinik özellikleri açısında istatistiksel olarak anlamlı bir fark bulunmadı (p>0,05). Grup içi değerlendirmelerde kuvvetlendirme grubunda FIQ skoru (p=0,01), PUKİ skoru (p=0,01), VAS skoru (p=0,00), PANAS pozitif-negatif (p=0,01), 5-DOKT, TUG, VOUT (p=0,01) skorları ile SF-36 ölçeğinin bütün alt skorlarında anlamlı farklılık bulunmuştur. Germe-gevşeme grubunda PUKİ (p=0,01), SF-36 Fiziksel fonksiyon (p=0,01), SF-36 Rol Kısıtlaması (Fiziksel) (p=0,03), SF-36 Vitalite (Enerji) (p=0,01) ve SF-36 Mental Sağlık (p=0,01) alt skorlarında istatistiksel olarak anlamlı farklılık bulundu. Gruplar arası karşılaştırmada, BDE (p=0,03), VOUT (p=0,006) ile SF-36 Ağrı (p=0,04), Vitalite (Enerji) (p=0,00) ve Mental Sağlık (p=0,01) alt skorlarında istatistiksel olarak anlamlı farklılık bulundu. Fibromyalji hastalarında uygulanan farklı egzersiz içeriklerine sahip Tele-rehabilitasyon uygulamaları, sağlık durumu, ağrı, uyku kalitesi, depresyon, duygu-durum, fiziksel performans ve yaşam kalitesi sonuçlarını olumlu etkilemektedir. Kas kuvvetlendirme egzersizleri verilen grupta diğer gruplara göre yaşam kalitesi ve depresyon yönünden; germe- gevşeme egzersizi verilen grupta ise esneklik yönünden daha fazla iyileşme olduğu gözlenmiştir. Kliniğe ulaşımın zor olduğu durumlarda Tele-rehabilitasyon uygulaması faydalı ve güvenli bir tedavi seçeneği olarak tercih edilebilir.

Anahtar Kelimeler: Fibromiyalji, Tele-rehabilitasyon, Fiziksel Aktivite, Egzersiz, Kuvvetlendirme, Germe, Gevşeme Egzersizi

Abstract

It was aimed to investigate the effect of Tele-rehabilitation application on the symptoms of the disease in patients with fibromyalgia. The cases were randomized into three groups as strengthening (n=20), stretching-relaxation (n=20) and control (n=20). The study was terminated with 55 people. In all cases; Fibromyalgia Impact Inquiry Scale (FIQ), Visual Analogue Scale (VAS), Quality of Life Scale (SF-36), Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI) and Positive-Negative Affect Scale (PANAS), 5 The Sit-to-Go Test (5-TSBS), Timed Up and Go Test (TUG) and V-Sit-Reach Test (VSR) were used. There was no statistically significant difference in terms of demographic and clinical characteristics of the groups (p>0,05). The intragroup assessment showed that in strengthening group, FIQ score (p=0,01), PSQI score (p=0,01), VAS score (p=0,00), PANAS positive-negative (p=0,01), 5-TSBS, TUG, VSR (p=0,01) scores and all sub-scores of the SF-36 scale were found to be significantly different. In the stretching-relaxation group, PSQI (p=0,01), SF-36 Physical function (p=0,01), SF-36 Role Restriction (p=0,03), SF-36 Vitality (p=0,01) and SF-36 Mental Health (p=0,01) sub-scores were found to be statistically significant. In comparison between groups, BDI (p=0,03), VSR (p=0,006) and SF-36 Pain (p=0,04), Vitality (p=0,00) and Mental Health (p=0,01) sub-scores were found to be statistically significant. Tele-rehabilitation applications with different exercise contents applied in patients with fibromyalgia positively affect the health status, pain, sleep quality, depression, mood, physical performance and quality of life results. In terms of quality of life and depression in the group given muscle strengthening exercises compared to the other groups; In the group that was given stretching-relaxation exercise, more improvement was observed in terms of flexibility. In cases where access to the clinic is difficult, Tele-rehabilitation application can be preferred as a useful and safe treatment option.

Keywords: Fibromyalgia, Tele-rehabilitation, Physical Activity, Exercise, Strengthening, Stretching, Relaxation Exercise

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1. Giriş

COVID-19 virüsü ilk olarak Aralık 2019'da Wuhan'da ortaya çıkan insanlarda ciddi solunum yolu hastalığına ve zatürre benzeri enfeksiyona neden olan yeni tip bir virüstür (1). 6 Ocak 2021 itibariyle Dünya Sağlık Örgütü 84.780.171 onaylı vaka ve 1.853.525 ölüm rapor etmiştir. ABD, İspanya, İtalya, Fransa, Almanya, İngiltere, Türkiye, Çin, İran ve Rusya pandemiden en çok etkilenen ülkelerin başında gelmektedir. (2). Pandemi koşulları nedeni ile sağlık hizmetlerine ulaşımda aksamalar yaşanması, kronik hastalığı olan bireylerin tedavi süreçlerini olumsuz yönde etkilemekte ve hastalığa bağlı komplikasyonların artmasına neden olabilmektedir. (3).

Süreklilik gerektiren tedavilerde salgın koşullarından kaynaklı aksamalar nedeniyle fiziksel ve biyopsikososyal durumun olumsuz etkilendiği hastalıklardan birisi de "Fibromiyalji (FM)"dir (4). FM, yaygın kas ağrısı ve yumuşak doku hassasiyeti ile karakterize kronik hastalıktır (5). FM genellikle yaşam kalitesini önemli ölçüde etkileyen ağrı, disabilite, uyku bozuklukları, anksiyete, bilişsel işlev bozukluğu ve depresif ataklar ile ilişkilidir (5). Fiziksel aktivitedeki azalma ve sosyal izolasyonun da eklenmesi ile hastalıkla ilişkili fiziksel ve psikolojik semptomlarda artış beklenmektedir.

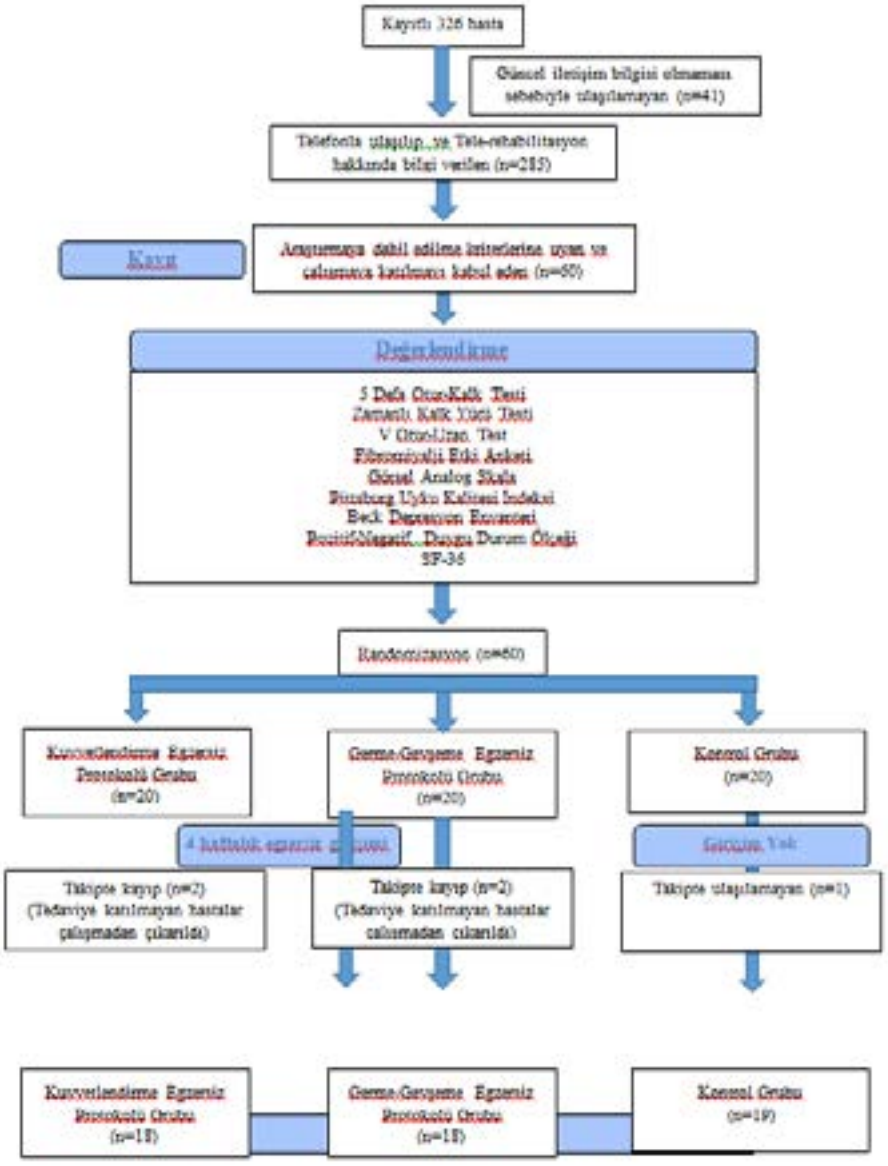
Fibromiyalji gibi kronik hastalığa sahip olan hastaların aksayan tedavi süreçlerini düzenlemek için etkili olabilecek uygulamalardan birisi, önceki salgınlarda (EBOLA, SARS, vb) etkinliği ispatlanmış olan, hasta takip ve tedavisinin uzaktan yapıldığı "Tele-rehabilitasyon" uygulamasıdır (6). Tele-rehabilitasyon, 'Tele-sağlık' teknolojileri içerisinde yer alan bilgi ve iletişim teknolojileri yoluyla rehabilitasyon hizmetlerinin sağlanması anlamına gelmektedir. Tele-rehabilitasyon hizmetleri içerisinde; değerlendirme, takip, önleme, müdahale, denetim, eğitim, danışmanlık yer almaktadır (7). Tele-rehabilitasyonun, klinisyenlere kolaylık sağlamasının yanında maliyet ve zaman tasarrufu da sağlamaktadır (8). Hastalıkların değerlendirme ve tedavisinde tele-rehabilitasyonun etkinliğine yönelik kanıta dayalı sonuçlara ihtiyaç duyulmaktadır (6,7).

Bu amaçla çalışmamızda, fibromyalji tanılı hastalarda Tele-rehabilitasyon yoluyla yaptırılacak egzersizlerin; ağrı, fonksiyonel kapasite, depresyon ve uyku kalitesi üzerine etkisini araştırmayı amaçladık.

2. Gereç ve Yöntemler

Çalışma, randomize kontrollü olarak tasarlanmış olup Trakya Üniversitesi Sağlık Uygulama ve Araştırma Merkezi Fizik Tedavi ve Rehabilitasyon Anabilim dalında yürütülmüştür. Çalışmamıza, COVID-19 virüs salgınının Türkiye'de bildirilen ilk vaka tarihi olan 23 Mart 2020 öncesinde Fiziksel Tıp ve Rehabilitasyon Polikliniği'ne yaygın ağrı şikayeti ile başvuran ve Amerikan Romatizma Birliği (9) kriterlerine uygun olarak FM tanısı almış olan kadın olgular dahil edildi. Yaşları 18-45 arasında olan, COVID-19 virüs salgını nedeni ile kliniğe tedavi amaçlı gelemeyen, online egzersiz eğitimine erişim imkanına ve bilgisine sahip olan olgular çalışmaya dahil edildi. İnflamatuvar ağrısı olmak, Diabetes Mellitus, kollojen doku hastalıkları gibi sekonder fibromyaljiye sebep olabilecek hastalıklara, fiziksel aktivite yapmasına engel ortopedik, nörolojik bir hastalığa, denge bozukluğuna sahip olmak, daha önce depresyon tanısına yönelik ilaç tedavisi almış olmak ise dışlanma kriterleri olarak belirlenmiştir. Çalışma "Helsinki Deklarasyonu" ilkelerine uygun olarak yürütülmüş olup, etik kurul onayı Trakya Üniversitesi Tıp Fakültesi Dekanlığı Araştırma Etik Kurulu'ndan 24.08.2020 tarihinde alınan kararla verilmiştir (No: TÜTF-BAEK 2020/305). Çalışmaya katılan tüm bireylerden bilgilendirilmiş gönüllü olur formu ve yazılı izinleri alındı. Çalışma için, Trakya Üniversitesi Sağlık Uygulama ve Araştırma Merkezi Fizik Tedavi ve Rehabilitasyon Anabilim Dalı'nda fibromiyalji teşhisi ile kayıtlı 326 kadın hastanın 285'ine telefonla ulaşıldı ve Tele-rehabilitasyon hakkında bilgi verildi. Dahil edilme kriterlere uyan ve çalışmaya katılmaya gönüllü 60 olgu ile araştırmaya başlanıldı. Tedavi öncesi hastalar video konferans yöntemi ile birebir değerlendirildi. Tedavi seanslarına katılamayan ve değerlendirmeye katılmayan toplam 5 olgu çalışma dışı bırakıldı ve çalışma 55 kişi ile tamamlandı.

Araştırmanın akış diyagramı Şekil 1'de yer almaktadır.



Şekil 1. *Akış diagramı*

Değerlendirme Yöntemleri

Çalışmaya katılacak olguların demografik ve klinik özellikleri "olgu takip formu" ile değerlendirildi. Fibromyalji hastaları için, fibromyaljinin kişiyi ne ölçüde etkilediğini değerlendirmek için Fibromyalji Etki Sorgulama Ölçeği (10) kullanıldı. Olguların ağrı değerlendirmesinde Görsel Analog Skala (VAS) (11), sağlıkla ilişkili yaşam kalitelerinin değerlendirmesinde amacı ile Yaşam Kalitesi Ölçeği (SF-36) (12) kullanıldı. Olguların depresyon durumu Beck Depresyon Envanteri (13) ile, uyku bozukluğu ise Pittsburgh Uyku Kalite İndeksi (PUKİ) (14) ile değerlendirildi. Ayrıca bireylerin duygu

durumu değişiklikleri Pozitif -Negatif Duygu Durumu Ölçeği ile değerlendirildi (15,16). Olguların fonksiyonel kapasitesinin değerlendirmesinde Zamanlı Kalk ve Yürü Testi (TUG) (17), 5 Defa Otur Kalk Testi (18) ve V-Otur-Uzan Esneklik Testi (19) kullanıldı. Değerlendirmelerin tümü tedavi öncesi ve sonrası olmak üzere iki kez, online ortamda, fizyoterapist kontrolünde yapıldı.

Tedavi Protokolü

Çalışmada uygulanacak egzersizlerin seçiminde American College of Sports Medicine (ACSM) kılavuzları kullanıldı (20). Fibromiyalji tanısı almış hastalar üç gruba ayrıldı. Birinci gruptaki olgulara kuvvetlendirme egzersizleri, ikinci gruptaki olgulara germe-gevşeme egzersizleri uygulandı. Üçüncü gruptaki olgular ise kontrol grubu olarak ayrıldı ve herhangi bir egzersiz verilmedi. Çalışmaya katılacak olguları için, internet ortamında uygulanabilecek şekilde egzersiz protokolleri oluşturuldu. Egzersizler; global postural reedikasyon yönteminin kas zincirlerindeki rolleri için büyük kaslara yönelik seçildi. Hastaların egzersiz programına Zoom uygulaması üzerinden katılması ve fizyoterapist eşliğinde egzersizleri yapması istendi.

Kuvvetlendirme Egzersiz Grubundaki katılımcılar; FM için ACSM kılavuzunda yer alan orta şiddette kuvvetlendirme egzersiz önerileriyle uyumlu olarak video bazlı olarak online uygulanan ve denetlenen bir programa alındı (21). Her egzersiz seansı; 10 dakika düşük yoğunluklu hareketler ve dinamik germe içeren aktif bir ısınma, 40 dakika orta-yüksek yoğunluklu video bazlı kuvvetlendirme antrenmanı ve düşük yoğunluklu hareketler ile 10 dakika dinamik ve statik germe içeren bir soğuma programından oluşturuldu. Egsersizler; kuadriseps, el bileği fleksörleri/ekstansörleri, pektoralis majör, rhomboidler, triseps surae ve kalçına fleksör/adduktör/abduktör kaslarına yönelik uygulandı. İlk 3 seansta direnç/ağırlık kullanılmadı. Kuvvetlendirme eğitimi, tipik olarak her egzersiz maksimum 2-3 set, en az bir set 8-12 tekrar yoğunluğunda olacak şekilde düzenlendi (22). Ağırlık artışı haftada 0.5 kg olarak yapıldı.

Germe-Gevşeme Egzersiz Grubundaki katılımcılara; ACSM'nin önerdiği fleksibilite egzersizleri uygulandı (23). Germeler 10-30 saniye süreyle, yoğunluğu hafif bir rahatsızlık noktasına kadar olacak şekilde, 3 tekrarla başlatılarak, hastanın durumuna göre 5 tekrara çıkıldı. Germe egzersizleri; paravertebral, gluteual, hamstring, kalça adduktörleri, lattisimus dorsi, pektoralis majör, triseps surae kaslarına yönelik olacak şekilde uygulandı (22).

Egzersiz programı 4 hafta boyunca haftanın 3 günü ve her egzersiz seansı 45-60 dakika olacak şekilde planlandı.

İstatiksel analiz

Veriler, tanımlayıcı ve çıkarımsal istatistikler kullanılarak analiz edildi. Anlamlılık düzeyi $p < 0,05$ olarak belirlendi. Veriler, SPSS kullanılarak analiz edildi. Değişkenler, Shapiro-Wilk testi kullanılarak normallik açısından test edildi. Başlangıçta, gruplar arasındaki değişkenlerdeki farklılıkları test etmek için tek yönlü varyans analizi (ANOVA), Kruskal-Wallis ve x2 testleri yapıldı. Normal dağılıma sahip sonuç ölçümleri için gruplar içinde müdahale öncesi ve sonrası farklılıkları saptamak için Paired T-Test kullanıldı; normal dağılmayan sonuç ölçümleri için Wilcoxon testi kullanıldı. Tedavi öncesi ve sonrası, gruplar arası karşılaştırmalar tek yönlü ANOVA ve Kruskal-Wallis testleri kullanılarak gerçekleştirildi; post-hoc analizi Tukey HSD ve Benferroni testleri kullanılarak gerçekleştirildi.

Çalışmamızın örneklem büyüklüğünün hesaplanmasında Harvard Üniversitesi güç analiz programı kullanılmıştır (24). Her grup için hastanın örneklem büyüklüğü 'Fibromyalji Etki Anketi (FIQ)' sonuç ölçütü olarak kullanılmasıyla elde edilen tahminlere dayandırılmıştır. Tedavi öncesi ve sonrasında FIQ toplam skorunda 15 puanlık bir değişim skorunun 0,95 puanlık etki büyüklüğü, 0,05 tip I hata ve %93 güç ile anlamlı olarak belirlenebilmesi için çalışmaya dahil edilecek olgu sayısı toplam 50 olarak bulunmuştur

(25). Çalışma sırasında oluşabilecek kayıplar göz önüne alınarak 58 katılımcı araştırmaya dahil edilmiştir.

3. Bulgular

Araştırma gruplarında yer alan hastaların demografik ve klinik özelliklerinin benzer olduğu ve gruplar istatistiksel olarak anlamlı bir farkın olmadığı belirlendi (p>0.05) (Tablo 1).

Tablo 1. Çalışma gruplarının demografik ve klinik özellikleri

Karakteristik özellik	Kuvvetlendirme Grubu (n=18) Ort. (%)	Germe-Gevşeme Grubu (n=18) Ort. (%)	Kontrol Grubu (n=19) Ort. (%)	p*
Yaş	49 (35-57)	43,5 (27-53)	46 (27-58)	0,172
Boy(m)	1,60 (1,57-1,70)	1,60 (1,55-1,68)	1,61 (1,56-1,70)	0,109
Kilo(kg)	71,5 (52-100)	65,5 (51-93)	63,5 (50-107)	0,092
VKİ (kg/m^2)	27,84 (20,31-35,55)	24,4 (21,23-36,33)	24,2 (18,37-41,28)	0,391
Eğitim Seviyesi	6 (%33,3)		6 (%33,3)	0,570
İlköğretim	6 (%33,3)	0	3 (%16,7)	
Ortaöğretim	0	14 (%77,8)	0	
Lise	5 (%27,8)	0	4 (%22,2)	
Lisans	1 (%5,6)	3 (%16,7)	5 (%27,8)	
Lisansüstü		1 (%5,6)		

Kısaltmalar: VKİ, Vücut Kitle İndeksi; p: Ki-Kare*

Grup içi değerlendirmelerde; kuvvetlendirme grubunda FIQ (p=0,01), VAS (p=0,002), PUKİ (p=0,01), BDE (p=0,002) ve PANAS pozitif-negatif (p=0,01) skorlarında istatiksel olarak anlamlı bir ilerleme gözlendi. Germe-gevşeme grubunda ise; sadece PUKİ (p=0,01) ve PANAS pozitif (p=0,01) skorlarında istatiksel olarak anlamlı bir gelişme gözlenirken, VAS, BDE ve PANAS negatif skorlarında istatiksel olarak anlamlı fark saptanmadı (p>0.05). Kontrol grubunda ise sadece PANAS negatif skorunda istastiksel olarak anlamlı fark mevcuttu (p=0.01) (Tablo 2,4). Gruplar arası değerlendirmede; BDE skorunda kuvvetlendirme grubu lehine istatiksel olarak anlamlı fark saptandı (p=0,01) (Tablo 2).

Tablo 2. Olguların Fibromyalji Etki Skoru, ağrı, uyku kalitesi, depresyon ve duygu durum skorlarının grup içi ve gruplar arası karşılaştırılması

Parametreler	Grup	Tedavi Öncesi M(min-maks) Ort ± SS	Tedavi Sonrası M(min-maks) Ort ± SS	Grup içi Değişim	Gruplar Arası Fark
Fibromyalji Etki Skoru (FIQ)	Kuvvetlendirme Grubu	57,41±20,06	42,04±20,97	**0,01** [pt]	
	Germe-Gevşeme Grubu	55,46±15,60	51,39±15,58	0,78	
	Kontrol Grubu	52,58±18,52	54,80±17,22	0,206	0,10
Vizüel Ağrı Skoru (VAS)	Kuvvetlendirme Grubu	6(3-10)	4,0(2,0-9,0)	**0,002** [wc]	
	Germe-Gevşeme Grubu	5,5(3-9)	5(0-10,0)	0,51	
	Kontrol Grubu	5(2-8)	5(2-10)	0,58	0,393
Pittsburg Uyku Kalite İndeksi (PUKİ)	Kuvvetlendirme Grubu	8,28±4,59	4,67±3,10	**0,01** [pt]	
	Germe-Gevşeme Grubu	7,55±3,58	5,11±2,45	**0,01** [pt]	
	Kontrol Grubu	7,22±4,15	6,61±2,99	0,219	0,113
Beck Depresyon Envanteri (BDE)	Kuvvetlendirme Grubu	14,39±5,66	9,67±5,58	**0,002** [pt]	
	Germe-Gevşeme Grubu	15,05±5,28	13,78±4,49	0,83	
	Kontrol Grubu	13,67±6,94	14,27±6,40	0,465	**0,03** [a]
Pozitif ve Negatif	Kuvvetlendirme Grubu	24,94±6,31	29,55±4,79	**0,01** [pt]	

Duygu Durum Ölçeği (PANAS) (Pozitif)	Germe-Gevşeme Grubu	25,78±4,54	28,39±3,63	**0,01** [pt]	0,127
	Kontrol Grubu	27,05±6,40	26,33±5,53	0,61	
Pozitif ve Negatif Duygu Durum Ölçeği (PANAS) (Negatif)	Kuvvetlendirme Grubu	23(12-36)	22,5(10-33)	**0,01** [wc]	0,755
	Germe-Gevşeme Grubu	23(13-36)	23(13-32)	0,107	
	Kontrol Grubu	22(13-33)	23(14-35)	**0,013** [wc]	

Kısaltmalar: Ort. ± SS; Ortalama±Standart Sapma
M (min-maks); Medyan (Minimum-Maksimum)
[pt] ; p<0.05 Grup içi karşılaştırma Paired T test
[wc] ; p<0.05 Grup içi karşılaştırma Wilcoxon
[a]; p<0.05 Gruplararası karşılaştırma ANOVA,
[kw] ; p<0.05 Gruplararası karşılaştırma Kruskall Wallis

Grup içi fiziksel performansın değerlendirmesinde; kuvvetlendirme egzersizleri grubunda 5-DOKT, TUG veVOU testlerinin tümünde (p=0,001), germe-gevşeme egzersizleri grubunda sadece VOUT'de istatiksel olarak anlamlı düzelme saptandı (p=0,001). Kontrol grubunda ise istatistiksel olarak anlamlı bir fark saptanmadı (p>0.05). Gruplar arası değerlendirmede ise sadece VOUT'de germe-gevşeme egzersizleri uygulanan grup lehine anlamlı fark bulundu (p=0,00) (Tablo 3).

Tablo 3.Olguların fiziksel performanslarının grup içi ve gruplar arası karşılaştırılması

	Grup	Tedavi Öncesi Ort ± SS M (min-maks)	Tedavi Sonrası Ort ± SS M (min-maks)	Grup İçi Değişim	Gruplar Arası Fark
5 Defa Otur-Kalk Testi (5 – DOKT)	Kuvvetlendirme Grubu	8,87(6,60-14,96)	7,28(5,86-12,11)	**0,01** [wc]	0,176
	Germe-Gevşeme Grubu	8,52(6,56-10,16)	7,82(6,15-9,76)	0,06	
	Kontrol Grubu	7,70(6,45-10,78)	7,44(6,40-9,99)	0,05	
Zamanlı Kalk Yürü Testi (TUG)	Kuvvetlendirme Grubu	7,35(6,45-9,85)	6,14(5,16-8,,59)	**0,01** [wc]	0,05
	Germe-Gevşeme Grubu	7,41(5,69-10,35)	6,70(5,68-10,29)	0,51	
	Kontrol Grubu	7,44(6,75-9,56)	7,42(6,39-10,33)	0,913	
V Otur-Uzan Testi (VOUT)	Kuvvetlendirme Grubu	5,33±6,61	8,72±5,33	**0,01** [pt]	**0,006** [a]
	Germe-Gevşeme Grubu	2,89±5,55	7,22±4,58	**0,01** [pt]	
	Kontrol Grubu	3,50±5,27	3,50±5,05	1,00	

Kısaltmalar: Ort. ± SS; Ortalama±Standart Sapma
M (min-maks); Medyan (Minimum-Maksimum)
[pt] ; p<0.05 Grup içi karşılaştırma Paired T test
[wc] ; p<0.05 Grup içi karşılaştırma Wilcoxon
[a] ; p<0.05 Gruplararası karşılaştırma ANOVA,
[kw] ; p<0.05 Gruplararası karşılaştırma Kruskall Wallis

Yaşam kalitesinin grup içi değerlendirmesinde kuvvetlendirme grubunda SF-36'nın tüm alt parameterelerinde istatistiksel olarak anlamlı iyileşme saptandı (p>0.05). Germe-gevşeme grubunda ise fiziksel fonksiyon (p=0.01), rol kısıtlaması (fiziksel) (p=0.03), vitalite (enerji) (p=0.00) ve mental sağlık skorlarında istatiksel olarak anlamlı fark vardı (p=0.01). Kontrol grubunda ise; sadece vitalite (enerji) (p=0.001) alt paramesinde istatiksel olarak anlamlı fark saptanmıştır. Gruplar arası değerlendirmede; ağrı (p=0.045), vitalite (enerji) (p=0.007) ve mental sağlık alt parametrelerinde kuvvetlendirme grubu lehine istatiksel olarak anlamlı fark gözlendi (p=0.01) (Tablo 4). Müdahale sırasında hiçbir katılımcı kas-iskelet sistemi hasarı veya fibromiyaljiye bağlı semptomlarda şiddetlenme problemi yaşamamıştır.

Tablo 4. SF-36 Ölçeği'nin grup içi ve gruplar arası karşılaştırılması

SF-36	Grup	Tedavi Öncesi Ort ± SS M (min-maks)	Tedavi Sonrası Ort ± SS M (min-maks)	Grup içi Değişim	Gruplararası Fark
Fiziksel fonksiyon	Kuvvetlendirme Grubu	45,28±23,73	69,72±15,95	**0,01** [pt]	
	Germe-Gevşeme Grubu	50,55±25,95	60,55±20,14	**0,01** [pt]	0,258
	Konrol Grubu	58,05±19,03	59,44±19,84	0,482	
Rol kısıtlaması (Fiziksel)	Kuvvetlendirme Grubu	12,5(0-100)	75(25-100)	**0,001** [wc]	
	Germe-Gevşeme Grubu	50(0-100)	50(0-100)	**0,033** [wc]	
	Konrol Grubu	37,5(0-100)	37,5(0-100)	0,655	0,144
Ağrı	Kuvvetlendirme Grubu	39,03±25,81	64,02±18,67	**0,01** [pt]	
	Germe-Gevşeme Grubu	49,17±25,99	53,61±22,21	0,39	**0,045** [a]
	Konrol Grubu	46,39±26,71	45,83±22,81	0,842	
Sağlığın genel olarak algılanması	Kuvvetlendirme Grubu	34,17±17,08	40,55±13,71	**0,01** [pt]	
	Germe-Gevşeme Grubu	44,17±20,81	46,67±21,96	0,24	
	Konrol Grubu	39,44±20,64	38,61±19,83	0,269	0,414
Vitalite (Enerji)	Kuvvetlendirme Grubu	45,55±19,92	64,17±13,85	**0,01** [pt]	
	Germe-Gevşeme Grubu	40,00±18,07	50,28±13,98	**0,01** [pt]	
	Konrol Grubu	42,22±20,88	48,61±18,13	**0,01** [pt]	**0,007** [a]
Sosyal fonksiyon	Kuvvetlendirme Grubu	75(25-100)	87,5(62,5-100)	**0,002** [wc]	
	Germe-Gevşeme Grubu	75(25-100)	81,25(25,100)	0,083	
	Konrol Grubu	75(25-100)	75(25-100)	0,705	0,100
Rol kısıtlaması (Emosyonel)	Kuvvetlendirme Grubu	0(0-100)	66,66(0-100)	**0,001** [wc]	
	Germe-Gevşeme Grubu	33,33(0-100)	33,33(0-100)	0,206	
	Konrol Grubu	33,33(0-100)	33,33(0-100)	0,655	0,053
Mental sağlık	Kuvvetlendirme Grubu	49,78±12,81	63,50±10,43	**0,01** [pt]	
	Germe-Gevşeme Grubu	49,78±8,48	56,44±7,87	**0,01** [pt]	
	Konrol Grubu	50,20±10,99	48,44±9,88	0,190	**0,01** [a]

Kısaltmalar: Ort. ± SS; Ortalama±Standart Sapma
M (min-maks); Medyan (Minimum-Maksimum)
[pt] ; p<0.05 Grup içi karşılaştırma Paired T test
[wc] ; p<0.05 Grup içi karşılaştırma Wilcoxon
[a] ; p<0.05 Gruplararası karşılaştırma ANOVA,
[kw] ; p<0.05 Gruplararası karşılaştırma Kruskall Wallis

4. Tartışma

Fibromiyalji tanılı olgularımıza dört hafta süresince haftanın üç günü fizyoterapist eşliğinde video konferans tabanlı kuvvetlendirme ve germe-gevşeme egzersizleri verilmiş ve sonuçlar kontrol grubu ile de karşılaştırılmıştır. Kuvvetlendirme eğitimi FM semptomlarını, ağrıyı, uyku kalitesini, yaşam kalitesini, fiziksel performansı, depresyon ve duygu durumu düzeyini önemli ölçüde geliştirmiştir. Kas kuvvetlendirme egzersizleri verilen grupta diğer gruplara göre yaşam kalitesi ve depresyon yönünden; germe- gevşeme egzersizi verilen grupta ise esneklik yönünden daha fazla iyileşme olduğu gözlenmiştir.

Tele-rehabilitasyon; mesafe, zaman ve maliyet engellerini en aza indirerek hastalara ve klinisyenlere hizmet vermek için teknolojiyi kullanarak rehabilitasyon hizmeti sunmanın pratik bir yöntemidir. Fizyoterapi de dahil olmak üzere sağlık müdahalelerinin kapsamını artırmanın bir yoludur ve sağlık sistemlerinde giderek daha fazla uygulanmaya başlamıştır. SARS-CoV-2 enfeksiyonunun geniş ve ani yayılmasının getirdiği yeni durum, sağlık profesyonellerinin rehabilitasyon programlarına devam etmesi gereken hastalara ulaşma yöntemlerini adapte etmelerini gerektirmiştir. Kombine ya da tek başına bir tedavi yöntemi olarak uygulanan

Tele-rehabilitasyonun etkinliği birçok kas-iskelet sistemi ağrısında araştırılmıştır (22). Bu alandaki meta-analiz ve klinik çalışmaların sonuçlarına ait kanıtlar; hastalarda ağrıyı azaltmak, fiziksel fonksiyonu, günlük yaşam aktivitelerini ve yaşam kalitesini arttırmak için yüz yüze müdahalelerin yerine Tele-rehabilitasyonun benimsenmesini önermektedir (26,27). Bu nedenle çalışmamızda FM hastalarında; hem değerlendirme hem de farklı tedavi yöntemlerini tele-rehabilitasyon yöntemi ile uygulayarak yöntemin etkinliğini araştırmayı planladık.

Fibromiyaljili hastalarda; klinik ortamlarda yaygın olarak kullanılan çok sayıda objektif değerlendirme parametreleri bulunmaktadır. Tele-rehabilitasyon yöntemleri ile yapılacak tedavilerde; bireylerin online olarak, kendi ev ortamlarında fiziksel, emosyonel düzeylerini, yaşam kalitelerini objektif ve kolay değerlendirme imkanı sağlayacak ölçüm yöntemlerinin kullanılmasına ihtiyaç duyulmaktadır. Çalışmamızın değerlendirme parametrelerinin bir bölümünü FM hastalarında sık kullanılan ve Türkçe geçerlilik ve güvenilirlikleri yapılmış ölçekler (10, 12-15), bir bölümünü ise video konferans yöntemiyle hem hasta tarafından uygulanması, hem fizyoterapist tarafından yönetmesi pratik ve objektif fiziksel fonksiyon ölçümleri (17-19) oluşturmaktadır. 5-DOKT, TUG ve VOU testinin fibromyaljide kullanılabilecek fiziksel performansa dayalı ölçüm yöntemlerinden olduğundan yola çıkarak çalışmamızda; VOU esneklik testinin esneklik sehpası gibi ek ekipman gerektirmeden ölçüm avantajı, 5-DOKT'nin uygulama pratikliği, TUG testi için gerekli 3 metrelik mesafenin kamera çekimi dahil ev içinde elde edilmesi mümkün bir mesafe olması sebebiyle tercih edilmiştir. Olgulardan; yaşam kalitesi, fonksiyonellik, duygu-durum, hastalık şiddeti gibi anket şeklindeki değerlendirme parametrelerini de online ortamda doldurmaları istenmiştir.

Assumpcao ve ark.; çalışmamıza benzer şekilde fibromiyalji hastalarında kuvvetlendirme ve germe-gevşeme egzersizlerinin etkinliğini kontrol grubu ile kıyaslamıştır (22). Çalışma ile parallelik gösteren araştırmamızın sonuçları da kuvvetlendirme egzersiz grubunun lehine ve germe-gevşeme grubu ise bazı parametrelerde kontrol grubundan üstün sonuçlara sahip olması sebebiyle benzerdir. Izquierdo-Alventosa ve ark. 8 hafta boyunca, düşük yoğunluklu kombine kuvvetlendirme ve aerobik egzersiz yaptırdıkları FM olgularında kontrol grubundaki olgulara göre 5-DOKT'da anlamlı ölçüde arttığını bildirmişlerdir (28). Jones ve ark. güçlendirme ve germe egzersizlerini tedavi öncesi ve sonrası verileri ile karşılaştırmıştır (29). Çalışmamızla paralel olarak; germe egzersizleri verilen grupta daha fazla esneklikte; kuvvetlendirme egzersizleri verilen grupta ise VAS ve FIQ skorlarında istatistiksel ve klinik olarak iyileşme gözlenmiştir. (29). Gruplar arası farklılıklar istatistiksel olarak anlamlı olmamasına rağmen, değişimin büyüklüğü genellikle güçlendirme grubu lehinedir. Bizim çalışmamızdan farklı olarak bu çalışmalarda değerlendirme ve tedaviler klinik ortamında yapılmasına rağmen benzer sonuçlar gözlenmesini tele-rehabilitasyonun etkin sonucuna bağlamaktayız.

Fibromiyaljide egzersizin yaşam kalitesine etkisi çeşitli programlarda araştırılmıştır. Jones ve ark. kuvvetlendirme ve germe egzersizlerini karşılaştırdıkları çalışmalarında her iki grupta da yaşam kalitesini önemli ölçüde arttığını bildirilmişlerdir (29). Bircan ve ark.; kuvvetlendirme ve aerobik egzersiz programının etkinliğinin karşılaştırıldığı çalışmalarında SF-36'nın tüm alt parametrelerinde grup içi değişim istatiksel olarak anlamlıyken grupların birbirine üstünlüğünün gözlenmediğini bildirdiler (30). Assumpcao ve ark. kuvvetlendirme ve germe egzersizlerinin kontrol grubuna karşı etkinliğinin karşılaştırıldığı çalışmalarının klinik analizinde; germe egzersizleri ağrı, yaşam kalitesi ve fiziksel fonksiyon yönünden; kuvvetlendirme egzersizleri ise depresyonu azaltma yönünden daha etkili bulunmuştur (22). Biz çalışmamızda SF-36'nın alt skorlarını incelediğimizde; yaşam kalitesinin kuvvetlendirme grubunda daha fazla arttığını söyleyebiliriz. Bu durumu aslında kas kuvvetinin artmasıyla hem fonksiyon hem de yaşam

Literatürde haftada 3-7 kez fiziksel egzersiz yapanlara kıyasla, hareketsiz kişilerin depresyon geliştirme riskinin önemli ölçüde daha yüksek olduğu bildirilmiştir (31). Borchers ve ark., FM'li hastalarda depresyon prevalansını %20-86 olarak bildirmişlerdir (32). FM'li hastaların, sağlıklı olgulara kıyasla depresyon geliştirme olasılığının daha yüksek olduğu bilinmektedir (33). Montoro ve ark., FM'li hastaların %47,2'sinde, sağlıklı olgularda ise yalnızca %7,9 oranında depresyon semptomlarının gözlendiğini bildirmişlerdir (33). FM hastalarında depresyon gelişme olasılığı yüksek olduğundan, fiziksel aktivite bu hastalardaki klinik tabloyu iyileştirmek için kaçınılmaz bir araçtır. Jones ve ark. kuvvetlendirme ve germe egzersizlerini karşılaştırdıkları çalışmalarının depresyon değerlendirmesinde BDE puanında germe grubuna göre kuvvetlendirme grubunda anlamlı değişiklikler meydana geldiğini; gruplar arası analizlerde ise farklılık gözlenmediğini bildirmişlerdir (29). Häkkinen ve ark. premenapozal fibromyaljili hastalar ile sağlıklı kadın olgularla yapılan 21 haftalık kuvvetlendirme egzersizlerinin uygulandığı çalışmalarında kontrol grubuna kıyasla BDE skoru yönünden deney grubunda anlamlı ölçüde düzelme olduğunu bildirmişlerdir (34). Biz de literatürle benzer şekilde depresyonun değerlendirilmesinde BDE skorunu kullandık. Çalışmamızda literatürde olduğu gibi kuvvetlendirme grubunda depresyonun azaldığını gözlemledik. Bunun yanında germe-gevşeme egzersizlerinin depresyon üzerinde etkisi olmadığını gözlemledik. Hastalık semptomlarının kuvvetlendirme egzersizleri verilen grupta daha fazla azaldığını gözlemledik. Kuvvetlendirme egzersizleri verilen grupta gördüğümüz depresyondaki azalmayı hastalık semptomlarındaki azalmaya bağlamaktayız.

Fibromyalji olgularının uyku bozuklukları prevelansınının %92.9 olduğu bildirilmektedir (35). Bu nedenle FM'li olgularda uyku bozukluğunun değerlendirilmesi önemlidir. Bircan ve ark., FM'li olgularda 8 hafta süresince uyguladıkları aerobik ve dirençli egzersizlerin etkinliğini karşılaştırdıkları çalışmada, iki grupta da önemli ölçüde uyku bozukluğunda düzelme olduğunu bildirdiler (30). Andrade ve ark.'nın haftada 3 kez, 24 seans kuvvetlendirme egzersizin etkinliğinin araştırıldığı çalışmalarında, PUKİ skorunda kontrol grubuna göre anlamlı ölçüde azalma sonucunu elde etmişlerdir (35). Çalışmamızda; uyku kalitesi hem kuvvetlendirme hem de germe-gevşeme egzersizleri verilen grupta düzeldi. Literatürle uyumlu olarak sonuçlarımız; egzersizin uyku bozukluğunu azaltmada etkili olduğunu göstermektedir.

Özellikle salgın sürecinde duygu-durum bozukluğu yaşanması beklediğimizden diğer çalışmalardan farklı olarak FM'li olgularda pozitif ve negatif duygu durumu değerlendirmesini de çalışmamıza dahil ettik. Her iki egzersiz grubunda da duygu durumunda olumlu yönde gelişme sağlandığını gözlemledik. Bu durum bize gösterdi ki, egzersiz yapmak hem salgın sürecinin getirmiş olduğu fiziksel inaktivitenin azalmasına hem de duygusal boyutta olumlu etkiler gözlenmesini sağlamaktadır.

Çalışmamızda fibromiyalji tanısı alan ancak düzenli bir tedavi programına ulaşma imkanına sahip olmayan olgular, Tele-rehabilitasyon yöntemi ile fizyoterapist eşliğinde birebir tedavi olma imkanına sahip oldular. İnternet tabanlı video konferans yöntemi ile yapılan tedavi ve değerlendirmelerin önemli bir artısı da olguların kendi ev ortamlarında sağlık hizmetlerine ulaşabilmeleri olmuştur. Ayrıca salgın sebebiyle nüfusu az olan kırsal bölgelerde yaşamayı tercih eden bireylerin de fizyoterapistlere erişimini sağlamada umut verici bir hizmet sunum modelidir. Tele-rehabilitasyon yöntemi ile tedavi; iş gücünde, maliyette ve zamanda tasarruf sağlayarak, rehabilitasyon hizmetlerinden her kesimden bireyin faydalanmasına olanak vermektedir. Çalışmamızın sonuçlarının; FM tanılı olgularda Tele-rehabilitasyon uygulamalarına olan ilgiyi arttıracağını ve bu konuda yapılacak ileri çalışmalara ışık tutacağını düşünmekteyiz. Çalışmamız zorunlu olarak evde kalınan COVID-19 salgını döneminde FM hastalarında Tele-rehabilitasyon yöntemiyle farklı egzersiz programlarının etkinliğinin araştırıldığı ilk çalışma olması

özelliğiyle de literatüre katkı sağlayacağını düşüncesindeyiz.

Çalışmamızda kuvvetlendirme egzersizlerini uygulayan grup her ne kadar kontrol grubuna göre kayda değer gelişme elde etse de sosyal izolasyon sonrası farkın devam edip etmeyeceğini bilmiyoruz. Ayrıca çalışmamızın egzersiz programının 4 hafta ile kısıtlı kalması ve uzun dönem takiplerimizin olmaması limitasyonlarımız arasındadır. Tedavi program bittikten sonra ev programı verilerek, uzun takiplerin yapıldığı; ayrıca ileri teknolojik imkanlar kullanıldığı çalışmaların planlanmasına ihtiyaç duyulmaktadır.

5. Sonuç

Fibromyalji tanılı olgularda uygulanan farklı egzersiz içeriklerine sahip Tele-rehabilitasyon uygulamaları, sağlık durumu, ağrı, uyku kalitesi, depresyon, duygu-durum, fiziksel performans ve yaşam kalitesi sonuçlarını olumlu etkilemektedir. Kas kuvvetlendirme egzersizleri verilen grupta diğer gruplara göre yaşam kalitesi ve depresyon yönünden; germe- gevşeme egzersizi verilen grupta ise esneklik yönünden daha fazla iyileşme olduğu gözlenmiştir. Küresel çapta tehlike yaratan ve bütün dünyada sosyal izolasyonu zorunlu kılan pandemi koşullarında teknolojinin sağladığı güvenli Tele-rehabilitasyon uygulamalarının yaygınlaştırılması ve geliştirilmesi, özellikle kronik rahatsızlığı bulunan bireylerin sağlık hizmetine ulaşımının sürekliliği bakımından oldukça önemlidir.

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Research Article / Araştırma Makalesi

Comparison of SLAP Lesions on MRI and Arthroscopy

SLAP Lezyonlarının MRG ve Artroskopik Karşılaştırması

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Abstract

Superior labrum anterior-posterior (SLAP) tears are a source of shoulder pain in orthopaedic patients. Magnetic resonance imaging (MRI) is a necessary tool for diagnosis in these patients. The aim of this study was to show correlation between MRI and arthroscopy evaluations of SLAP lesions. The study included a total of 52 patients, comprising 32 females and 20 males with a mean age of 50.40 years (range: 19-74 years) who underwent shoulder arthroscopy surgery for an existing shoulder pathology between April 2019- May 2020. The right shoulder was affected in 34 (65%) patients and the left in 18 (35%). The pre-operative diagnoses were rotator cuff syndrome (n:34), impingement syndrome (n:7), frozen shoulder (n:2) and Bankart lesion (n:9). MRI of the shoulder joint was applied followed by shoulder arthroscopy. Only SLAP type classifications were detected on arthroscopic examination and there were 13 Type 1 (33%), 23 (58%) Type 2, one (3%) Type 3, one (3%) Type 4, and one (3%) Type 5 lesion. SLAP lesions were detected on both MRI and arthroscopy in 12 patients. The lesion could not be detected arthroscopically in 3 patients although MRI reported a SLAP lesion. SLAP lesions were negative on both MRI and arthroscopy in 10 patients. In 27 patients, MRI was negative, but the SLAP lesions were detected in arthroscopy. In the diagnosis of SLAP lesions, MRI showed 31% sensitivity, 77% specificity, 80% positive predictive value, and 27% negative predictive value. The accuracy of MRI was found to be 42%. Reliability of agreement (Fleiss kappa) between MRI and arthroscopy was found to be 0.048 (p=0.596). Although MRI is a useful tool for diagnosing other shoulder pathologies, it is not sufficient for the detection of SLAP lesions compared to gold standard shoulder arthroscopy.

Keywords: Shoulder; SLAP lesion; Arthroscopy; MRI; Diagnosis; Sensitivity; Specificity

Özet

Superior labrum anterior-posterior (SLAP) yırtıkları ortopedi hastalarında omuz ağrısı kaynaklarındandır. Manyetik rezonans görüntüleme (MRG) bu hastalarda teşhis için gereklidir. Bu çalışmanın amacı SLAP lezyonlarının MRG ve artroskopi değerlendirmeleri arasındaki uyumu göstermektir. Çalışma Nisan 2019- Mayıs 2020 tarihleri arasında varolan omuz patolojisi için omuz artroskopi cerrahisine giden yaş ortalaması 50.40 (aralık: 19-74 yaş) olan, 32 kadın ve 20 erkek içeren toplam 52 hastadan oluşmaktadır. 34 hastada (%65) sağ, 18' nde (%35) sol omuz etkilenmişti. Hastalarda ameliyat öncesi teşhis; rotator kaf sendromu (n:34), impingement sendromu (n:7), donuk omuz (n:2) ve bankart lezyonu (n:9) idi. MRG yapıldıktan sonra omuz artroskopisi yapıldı. Sadece artroskopik değerlendirmede SLAP tip sınıflaması tespit edildi ve 13 Tip 1 (%33), 23 Tip 2 (%58), bir Tip 3 (%3), bir Tip 4 (%3) ve 1 Tip 5 (%3) lezyon mevcut idi. Oniki hastada hem MRG hemde artroskopi de SLAP lezyonları saptandı. MRG de SLAP lezyon olmasına rağmen 3 hastada artroskopik olarak lezyon saptanmadı. 10 hastada hem artroskopi hem de MRG de SLAP lezyonu yoktu. 27 hastada MRG de lezyon yok iken, artroskopi de lezyon saptandı. SLAP lezyonlarının teşhisinde, MRG %31 duyarlılık, %77 özgüllük, %80 pozitif öngörme değeri ve %27 negatif öngörme değeri gösterdi. MRG' nin doğruluğu %42 olarak bulundu. MRG ve artroskopi arasında anlaşmanın güvenilirliği (Fleiss kappa) 0.048 (p=0.596) olarak bulundu. MRG diğer omuz patolojilerini teşhis etmekte yararlı bir araç olmasına ragmen, altın standart olan omuz artroskopisine kıyasla SLAP lezyonlarını tespit etmekte yeterli değildir.

Anahtar Kelimeler: Omuz; SLAP lezyon; Artroskopi; MRG; Teşhis; Duyarlılık; Özgüllük

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1. Introduction

In 1985 Andrews et al. first described superior labral anterior-posterior (SLAP) lesions and, subsequently, Snyder et al. classified SLAP lesions (1,2). However, the diagnosis and treatment of SLAP lesions remains a huge challenge for shoulder surgeons. The long head of the biceps tendon is attached to the superior labrum and has a rich innervation which is responsible for pain whenever injury occurs (3). Snyder classified SLAP injuries into four types (types I–IV), based on arthroscopic findings (2). That classification was later expanded by Maffet et al. with three additional types (Table 1) (2,4,5). The most common SLAP lesion is Type 2, which represents 55% of all lesions in daily practice (6). Physical examination of these lesions has been shown to have poor diagnostic value when performed alone (7). Therefore, conventional magnetic resonance imaging (MRI) and magnetic resonance arthrography (MRA) have become increasingly used diagnostic tools in detecting both shoulder pain and SLAP lesions (8). Many studies in the literature have reported that MRA is the best visualization method for the diagnosis of these lesions (9,10). Although MRI is generally used for the diagnosis in daily practice, the gold standard for SLAP lesion diagnosis is shoulder arthroscopy (2). Nevertheless, in the diagnosis and classification of SLAP lesions, there may be inconsistencies between conventional MRI and shoulder arthroscopy, and therefore, the treatment plan and/or type of surgery may have to be changed during surgery whenever arthroscopy is used. When performing shoulder arthroscopy in our daily practice, SLAP lesions have been seen to differ from the preoperative MRI studies. Thus, it was decided to review both shoulder arthroscopic findings and MRI results for the absence or presence of SLAP lesions and classification. The aim of this study was to evaluate the effectiveness of MRI in the diagnosis of SLAP lesion in a population of subjects with and without multiple concomitant diagnoses with shoulder pain.

Table 1. Classification of SLAP lesions according to arthroscopy

SLAP Type (2,4,5)	Description of the lesion
1	Labral and biceps fraying, biceps anchor intact
2	Labral fraying with detachment of the superior labrum and biceps anchor
3	Bucket-handle tear of the superior labrum, biceps anchor is intact
4	Bucket-handle tear of the superior labrum with detached biceps tendon anchor
5	Type II SLAP lesion and Bankart type anterior labral tear
6	Type II SLAP lesion and an unstable flap tear of the labrum
7	SLAP lesion and capsular injury that extends anteriorly, inferior to the middle glenohumeral ligament
8	Type II SLAP with extension into the posterior labrum
9	Type II tear with circumferential labral disruption
10	Type II lesion with posterior labral disruption

2. Materials and Methods

This retrospective study was approved by the Ethics Committee of our University Hospital (Number: E-25403353-050.99-138972). The study included 52 patients with a shoulder pathology who underwent arthroscopic shoulder surgery between April 2019 and May 2020. All the physical examinations of the patients were performed by the first author in the outpatient clinic of our university hospital. After examination of all patients, shoulder MRI was requested. In 26 patients, shoulder MRI had been taken at a different centre, and if that was within the previous 3 months, additional MRI at our centre was not performed. Additional shoulder MRI was applied to 9 patients as more than 3 months had elapsed since the previous MRI examination. A total of 30 patients were excluded from the study because of previous arthroscopic shoulder surgery (n:6), shoulder fracture (n:8), known malignancy (n:2), and cervical discopathy/radiculopathy (n:14). The

remaining 52 patients were evaluated as the study group. The 52 patients comprised 32 (62%) females and 20 (38%) males with a mean age of 50.40 years (range: 19-74 years).

The MR images were obtained using a conventional 3 Tesla (T) MRI unit (Siemens) without contrast agent in all patients. In addition to routine sections, axial proton density weighted, T2-weighted sagittal and coronal sequences, and axial fat-suppressed T2-weighted images were obtained, and all the images were reviewed. In the patients with MRIs from a different centre, there were both 1.5 and 3 T shoulder MRI. Arthroscopic video records, surgery notes, and shoulder MRI views, were reviewed for all patients. The time interval between the MRI scan and arthroscopic surgery was less than 3 months in all patients. All surgeries were performed by the first author (CG). None of the patients included in the study had undergone previous shoulder surgery. Arthroscopic evaluation, diagnosis and treatment according to the existing pathology were successfully applied in all cases. All surgeries were performed under general anaesthesia in the beach-chair position. After review of the arthroscopic video records and preoperative shoulder MRIs, the sensitivity and specificity of MRI compared to gold standard shoulder arthroscopy, were calculated and accuracy was determined according to the following:

1. True positive (TP): MRI diagnosis of SLAP lesion, confirmed on arthroscopic evaluation.

2. True negative (TN): MRI diagnosis of no SLAP lesion was confirmed on arthroscopy.

3. False positive (FP): MRI showed a SLAP lesion but arthroscopy was negative.

4. False negative (FN): MR images were negative but arthroscopy showed a SLAP lesion.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS Statistics Version 22 software. As shoulder arthroscopy is accepted as the gold standard, compliance of both diagnostic methods was compared. Sensitivity, specificity, positive and negative predictive values of the MRI in diagnosis of SLAP lesions were calculated. Reliability of agreement between MRI and arthroscopy in the diagnosis of SLAP lesions was calculated using the Fleiss kappa test. A value of $p<0.05$ was considered to be statistically significant.

3. Results

The right shoulder was affected in 34 patients (65%) and the left shoulder in 18 (35%). The pre-operative diagnoses were rotator cuff syndrome (n:34), impingement syndrome (n:7), frozen shoulder (n:2) and Bankart lesion (n: 9). SLAP lesion types were seen on MRI views as presence of degeneration, tear, or normal. The SLAP type classifications detected on arthroscopic examination were 13 (33%) Type 1, 23 (58%) Type 2, one (3%) Type 3, one (3%) Type 4, and one (3%) Type 5 lesion.

In 12 of 52 patients, SLAP lesions were detected on both MRI and arthroscopy. SLAP lesions were negative on both MRI and arthroscopy in 10 patients. The lesion could not be detected arthroscopically in 3 patients although MRI reported a SLAP lesion. In 27 patients, MRI was negative but the SLAP lesions were detected in arthroscopy (Fig.1,2). In the diagnosis of SLAP lesions in this study, MRI showed 31% sensitivity, 77% specificity, 80% positive predictive value, and 27% negative predictive value (Table 2). Accuracy was found to be 42%. Reliability of agreement (Fleiss kappa) between MRI and arthroscopy was found to be 0.048 ($p=0.596$).

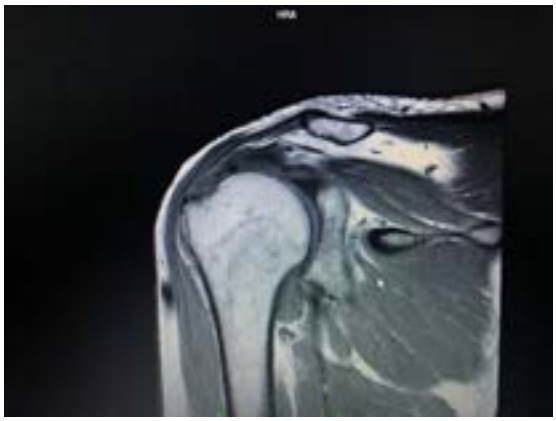

Figure 1. On the MRI, the SLAP lesion was not detected

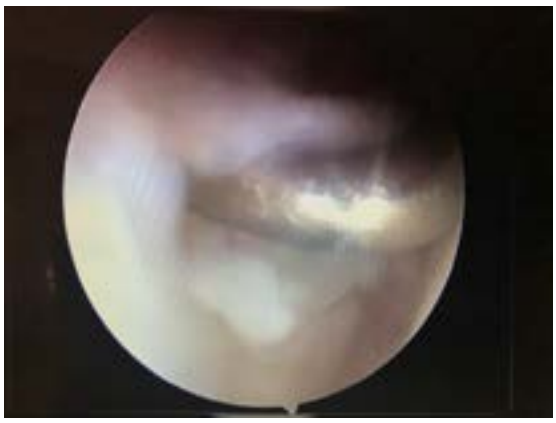

Figure 2. Type 2 SLAP lesion was seen on arthroscopy (False Negative)

Table 2. Sensitivity, specificity, positive and negative predictive values of MRI compared to gold standard shoulder arthroscopy

	Arthroscopy-Positive	Arthroscopy-Negative	Total
MRI-Positive	12 (23%)	3 (6%)	15 (29%)
MRI-Negative	27 (52%)	10 (19%)	37 (71%)
Total	39 (75%)	13 (25%)	52 (100%)

Sensitivitiy of MRI: TP/(TP+FN)= 12/39= 31%
Specificity of MRI: TN/TN+FP=10/13= 77%
PPV of MRI: TP/TP+FP=12/15= 80%
NPV of MRI: TN/TN+FN=10/37= 27%
Accuracy: (TP+TN)/(TP+TN+FP+FN)= 22/52= 42%

4. Discussion

SLAP lesions often cause shoulder pain, dysfunction, and instability. The classic definition of the SLAP lesion is known descriptively as a disruption of the superior labrum between the 10 to 2-o'clock positions of the superior part of the glenoid (2). SLAP injuries usually occur in throwing athletes and in the normal population with traction and/or compression injuries to the shoulder joint. In literature, different physical examination manoeuvres have been described for the identification of SLAP lesions. The O'Brien active-compression test, Kim test, Biceps load test, Crank test, Yergason and Speed tests are some examples of the tests used for detecting SLAP lesions in daily practice (11). These

examination tests only suggest the presence of SLAP pathology, and there is no single test which shows the high diagnostic accuracy. Moreover, these examinations do not fully diagnose SLAP lesions and they can be confused with other pathologies of the shoulder joint. Snyder et al. classified SLAP lesions as follows; Type I lesions; show degenerative changes to the glenoid labrum but an attached labrum to the glenoid rim. Type II lesions; show degenerative changes and fraying, as well as complete detachment of the labrum from the glenoid rim and instability of the biceps tendon attachment. Type III lesions; involve a displaced free margin of the labrum into the joint and an attached biceps tendon. Type IV lesions are categorized as a displaced labrum into the joint and an affected long biceps tendon injury (2). Surgical options for type 2 SLAP lesions include biceps tenodesis/tenotomy or repair of the SLAP lesion. Patients aged > 40 years have been reported to have worse functional results and higher failure rates after repair of these lesions (12). Therefore, in the current study, SLAP lesions were only repaired in younger patients.

Many studies have evaluated the accuracy of MRI for the diagnosis of SLAP lesions (Table 3) (8,13-18). Reported specificity has ranged from 69% to 99% and sensitivity from 75% to 98% (9). It was stated in one study that conventional MRI was not a suitable test for accurately diagnosing SLAP tears in patients with concomitant disorders who were not primarily overhead-throwing athletes (13). In contrast, Connell et al reported sensitivity of 98% and specificity of 89.5% in the detection of SLAP lesions on conventional MRI (14). Unlike the current study, the population of the Connell included athletes (79%), and therefore, can be considered not to reflect accurate results. MR and MR arthrography with 1.5-T and 3-T scanners are currently the mainstays of imaging used to diagnose SLAP lesions prior to arthroscopy. In the current study, both 1.5-T and 3-T MRI were used. MRI of the shoulder has been found to be a suitable method for the detection of labral tears, but it has been shown that a number of pathologies may be missed (19). Therefore, the use of Gadolinium to enhance the accuracy of MRI may advance the detection of SLAP lesions (20). Gadolinium-enhanced MRI was not used in the current study because the standardization and application of this technique is quite difficult in practice. It has also been reported that compared to arthroscopy, 3.0 T MRI of the shoulder is very specific and sensitive for the diagnosis of labral tears (10). However, according to the current study results, 3.0 T MRI was not closely correlated with arthroscopy for the detection of SLAP lesions. Most patients in this study group had 3.0 T MRI, but no correlation was determined of SLAP lesions with arthroscopy despite the use of 3.0 T MRI rather than 1 or 1.5 T MRI. Arthroscopy is the current gold standard for the diagnosis of shoulder pathologies. In previous studies, arthroscopic surgery has been used as the reference standard for a SLAP lesion (14). Arthroscopy has disadvantages in visualising the internal part of the tissues in the shoulder joint. Nevertheless, MRI also provides information in some fields not seen in arthroscopy, such as the internal structure of the rotator cuff. Field et al (22) stated that SLAP tears which have been arthroscopically confirmed, were inconsistent with preoperative MRIs. Liu et al (23) showed that physical examination for labral pathology was more accurate than MRI diagnosis for arthroscopically confirmed SLAP lesions. Snyder et al reported MRI reports from multiple centres for 73 patients with SLAP lesions. Only 26% of the radiologists' MRI reports suggested a SLAP lesion (6). In another study, it was shown that rotator cuff tears, Bankart lesions and osteochondral defects were detected on MRI more accurately than on the gold standard shoulder arthroscopy, although there were differences in the detection of SLAP lesions (24). There was also tremendous variation in the protocols for these MRI studies. Hence, the quality of many of these films in the current study may not have been consistent with the high and consistent standards present in the practices and in the studies of their peers in previous literature.

Table 3. Studies in the literature and current study

Reference number	Number of Patients	Specificity	Sensitivity	PPV	NPV	Accuracy	MRI Tesla (T)
Connell (14)	102	89	98	96	94	96	1.5
Legan (16)	88	99	75	-	-	95	1.5
Sheridan (8)	234	79-89	14-64	5-29	91-98	77-87	1.5
Philips (13)	77	4-22	83-91	63-70	11-53	85	1.5
Conolly (17)	144	94	38	90	51	61	1.5/3
Magee (15)	75	100	84	99	83	90	3
Yıldız (18)	132	40	71	80	29	64	1.5
Current study	52	77	31	80	27	42	1.5/3

PPV: positive predictive value, NPV: negative predictive value

The glenoid labrum shape is curved along the glenoid surface, so coronal images of MR are typically not oriented along the long axis of the glenoid, which limits the accuracy of the SLAP pathology (25-27). The probable reasons that SLAP lesions were either missed or misdiagnosed may be that the abnormalities were very small, and thus inadequate spatial resolution may caused them to go undetected (9). A good history and physical examination should still be considered most important in the diagnosis of shoulder pathologies in general. However, detecting SLAP lesions in this way is not as simple as for other pathologies of shoulder. MRI is helpful in diagnosing a shoulder pathology. It is also valuable in assessing the injury status and the severity when many structures are involved and it becomes difficult to show the exact pathology in the shoulder joint with clinical examination. However, it is difficult to diagnose SLAP lesions on conventional MRI. The radiologist's interpretation is an important factor in providing an accurate MRI diagnosis. Appropriate clinical assessment and providing detailed clinical findings to the radiologist, could improve the accuracy of MRI in the diagnosis of shoulder pathology. Both MRI and arthroscopy can be considered to have significant roles in the diagnosis of SLAP pathology. In shoulder arthroscopy, there is a long learning curve, although it is a safe procedure, cost effective, and the diagnosis is more accurate when compared to MRI. In the current study, the sensitivity and accuracy of MRI compared to gold standard arthroscopy was found to be 31% and 42%, respectively. These results were compared in Table 3 with those of other studies in the literature and it can be seen that, the sensitivity and accuracy values obtained in the current study were low compared to other data. These results were unique in respect of showing the lowest sensitivity results in the literature despite the highest use of 3T MRI. The importance of the current study can be considered to be the low values of sensitivity and accuracy of the MRI results obtained compared to gold standard arthroscopy. This could be attributed of missing properties of MRI.

There were some limitations to this study; 1) The patient sample size was not large enough to make a conclusive comment on this topic 2) MR arthrography was not used instead of MRI, because of the difficulty of application of arthrogram in usual outpatient clinic conditions.

5. Conclusions

Although the clinical examination and history are the main procedures to detect most

shoulder pathologies, the detection of SLAP lesions requires further examination. In the current study, the percentage rate of detection of SLAP lesions on MRI was not found to be as high as gold standard arthroscopy. Care should be taken in arthroscopy for the detection of real SLAP lesions, which have not been seen on conventional MRI. There is a need for further clinical studies of larger series, including both MRI and MR arthrography compared to arthroscopy, to be able to fully clarify this topic.

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Research Article / Araştırma Makalesi

Evaluation of Anthracycline Related Arterial Stiffness in Childhood Cancer Survivors

Çocukluk Çağı Kanser Sağ Kalanlarında Antrasiklin İlişkili Arteriyel Sertliğin Değerlendirilmesi

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Abstract

Childhood cancer survivors have a significantly increased risk of cardiovascular morbidity and mortality. Improved screening methods are needed for early detection of cardiotoxicity. The aim of the study is to evaluate arterial stiffness as an indicator of vascular damage by oscillometric pulse wave analysis in childhood cancer survivors. A total of 38 patients and 25 age and gender matched healthy volunteers were included in this cross-sectional single centre study. All participants, underwent evaluation of arterial stiffness through non-invasive measurement of hemodynamic parameters such as pulse wave velocity (PWV) and central systolic blood pressure (c-SBP) with the Mobil-O-Graph® pulse wave analysis device. Left ventricular ejection fraction (LVEF) and left ventricular mass index (LVMI) were obtained by M-mode echocardiography. The median age of the childhood cancer survivors was 12.5 (4.25-18) and the median duration time after end of chemotherapy was 36 (12-116) months. Both groups were statistically similar in age, body mass index, LVEF and LVMI. Childhood cancer survivors had significantly lower peripheral systolic blood pressure compared to controls. Average c-SBP and PWV were similar between groups. Childhood cancer survivors > 15 years old also had similar PWV value with those < 15 years old. There were no signs of arterial stiffness in childhood cancer survivors late after chemotherapy according to the ambulatory oscillometric PWA. Longer follow-up duration may be required to determination of subclinical vascular damage

Keywords: anthracyclines, arterial stiffness, cardiotoxicity, pulse wave velocity, vascular toxicity

Özet

Çocukluk çağı kanser sağ kalanlarının kardiyovasküler morbidite ve mortalite riski önemli ölçüde artmıştır. Kardiyovasküler toksisitenin erken tespiti için gelişmiş tarama yöntemlerine ihtiyaç vardır. Çalışmanın amacı, çocukluk çağı kanseri sağ kalanlarında osilometrik nabız dalga analizi ile vasküler hasarın bir göstergesi olan arteriyel sertliği değerlendirmektir. Bu kesitsel, tek merkezli çalışmaya toplam 38 hasta ve 25 yaş ve cinsiyet uyumlu sağlıklı gönüllü çalışmaya dahil edildi. Tüm katılımcılar Mobil-O-Graph® marka nabız dalga analizi cihazı ile nabız dalga hızı (PWV) ve merkezi sistolik kan basıncı (c-SBP) gibi hemodinamik parametrelerin invazif olmayan ölçümü yoluyla arteriyel sertliğin değerlendirmesine tabi tutuldu. Sol ventrikül ejeksiyon fraksiyonu (LVEF) ve sol ventrikül kitle indeksi (LVMI) M-mod ekokardiyografi ile ölçüldü. Çocukluk çağı kanseri sağ kalanlarının medyan yaşı 12,5 (4,25-18) ve kemoterapi bitiminden sonraki medyan süresi 36 (12-116) aydı. Her iki grup da yaş, vücut kitle indeksi, LVEF ve LVMI açısından istatistiksel olarak benzerdi. Çocukluk çağı kanseri sağ kalanları, kontrollere kıyasla daha düşük periferik sistolik kan basıncına sahipti. Ortalama c-SBP ve PWV gruplar arasında benzerdi. Onbeş yaşından büyük çocukluk çağı kanseri sağ kalanları, 15 yaşından küçüklerle benzer PWV değerine sahipti. Ambulatuar osilometrik PWA ile çocukluk çağı kanseri sağ kalanlarında kronik dönemde subklinik arteriyel sertlik bulgusu tespit edilmedi. Subklinik vasküler hasarın tespiti için daha uzun takip süresi gerekli olabilir.

Anahtar Kelimeler: antrasiklinler, arterial stiffness, kardiyak toksisite, nabız dalga hızı, vasküler toksisite

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1. Introduction

Anticancer treatments, including anthracyclines, alkylating agents, and vascular endothelial growth factor inhibitors, are associated with direct vascular damage and an increased risk of adverse vascular outcomes that can occur after the first treatment and persist into survival (1,2). Therefore, recent reports in the field of vascular cardio-oncology highlighted the critical need for continuous monitoring of vascular health during treatment and in survivors. Thus, primary and secondary treatment strategies can be developed to prevent vascular side effects. However, there are no systematic reports evaluating current clinical strategies that have been used to monitor vascular toxicity. This reflects a serious gap in our current knowledge of anthracycline-associated vascular injury and the need to identify potential imaging approaches.

Vascular damage results in an increase in the level of arterial stiffness defined as a decrease in the elastic property of the wall structure of the arteries. Arterial stiffness is a vascular biomarker describing the alterations of arterial properties which result in a reduction of the arterial wall elasticity, and therefore in a decrease of the buffering capacity of arteries to pulsatile cardiac ejection (3). Cancer patients and survivors have increased arterial stiffness more than the levels expected with aging (4,5). According to the results of the analysis of a total of 19 studies, the arterial stiffness level of cancer patients is higher both after treatment compared to baseline values and compared to healthy controls (6). Anthracyclines cause overexpression of inflammatory cytokines in endothelial cells and reduce production of endothelin and nitric oxide (NO) resulting in endothelial cells being more susceptible to apoptosis and the functional integrity of endothelium being compromised (7). All these mechanisms lead to a loss of the ability of endothelial cells to regulate the vascular smooth muscle tone and therefore arterial stiffness increases (3).

The gold standard method used for the assessment of arterial stiffness is pulse wave analysis (PWA). Non-invasive investigation of the PWV, via ultrasound or oscillometric methods, provides information on the elasticity of the vascular system and enables early recognition of damages in the vessels. Moreover, oscillometric PWA is a current and reliable method that has recently been used in children as well as in adults (8,9).

The aim of this study is to determine the subclinical evidence of anthracyclines related endothelial dysfunction by non-invasive ambulatory oscillometric PWA in childhood cancer survivors.

2. Methods

This is a cross-sectional and single-center study which was conducted with childhood cancer survivors who were received anthracycline chemotherapy and healthy controls. The control group consisted of healthy children, who were referred to the pediatric cardiology clinic and only diagnosed with innocent murmur and had no evidence of structural heart disease on echocardiography. Inclusion criteria were as follows; being older than six years old, having at least one year after chemotherapy, not having diabetes, hyperlipidemia, kidney, liver and structural heart diseases. This information was obtained from the parents and health records. All of the participants were evaluated in terms of structural and functional heart disease with two-dimensional and M-mode echocardiographic examination. The study protocol was approved by the Eskisehir Osmangazi University Ethics Committee (Approval number: E-25403353) and written informed consent was obtained from the parents of each child.

Echocardiographic examination

Transthoracic echocardiography was performed by one single experienced pediatric cardiologist using the commercially available equipment Affinity 70 (Philips Medical Systems, Bothell, WA, USA) with 2–4 and 4–8 MHz broadband probes. The participants were examined at rest while in the left lateral decubitus during sinus rhythm. Left ventricular internal dimensions (LVEDd), interventricular septum thickness (IVSDd), and posterior wall thickness (LVPWd) were measured at the end diastole using two-dimensional M-mode echocardiography

according to the pediatric guidelines of the American Society of Echocardiography (10). Left ventricular mass (LVM) was calculated according to the Devereux Formula and indexed to the heights. Left ventricular ejection fraction (EF) was calculated using the Teichholz formula (11,12).

Pulse wave analysis

Oscillometric PWA is an easy-to-apply, non-invasive and reliable method in the assessment of arterial stiffness and has been reported to be suitable for children (13). For pulse wave analysis and blood pressure monitoring, the Mobil-O-Graph (IEM, Industrielle Entwicklung Medizintechnik und Vertriebsgesellschaft mbH, Stolberg, Germany) device and ARCSolver pulse wave analysis software (AIT Austrian Institute of Technology GmbH, Vienna, Austria) were used. A 24-hour blood pressure monitoring was performed by connecting a cuff of a size appropriate for upper right arm circumference. As a result of the analysis, 24-hour peripheral and central blood pressure measurements, systolic and diastolic blood pressure loads, nighttime blood pressure reduction rates, pulse wave velocity and augmentation index measurements were obtained.

Statistical Analysis

The data were analyzed using SPSS 16.0 statistical software (SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used for assessment of normal distribution. All normally distributed data was shown appropriately as mean ± standard deviation, otherwise they were presented as median with range. Data was adequately evaluated according to their distribution by T-test or Mann-Whitney-U-Test. Correlations between variables were analyzed with Pearson's correlation for normally distributed variables and Spearman's who for non-normally distributed data. P-values of <0.05 were indicated as statistically significant.

3. Results

Thirty-eight patients who were received anthracycline treatment between 2007 and 2019 with the diagnosis of a childhood cancer at Eskisehir Osmangazi University Pediatric Hematology Clinic and 25 healthy children were included in the study. There was no significant difference between patients and controls in terms of age, gender and anthropometric measurements (p>0.05) (Table 1). The characteristic features of cancer survivors are specified in Table 2.

Table 1. Demographics of patients and controls.

Variable	Patients (n=38)	Controls (n=25)	P value
Age	12.5 (4.25-18)	11 (6.5-17)	0.513
Gender (female/male)	19/19	13/12	0.541
Weight, kg	43.93±14.95	41.1±15.75	0.522
Height, cm	146.43±18.58	148.32±16.24	0.681
BMI, kg/m^2	19.87±3.84	18.05±3.73	0.068

BMI, body mass index

Table 2. Characteristics of patients

Diagnosis (n)	
Hodgkin disease	1
Non-Hodgkin lymphoma (Burkitt, NHL, T-NHL)	3
Acute lymphoblastic leukemia (PreB-ALL, T-ALL, C-ALL)	29
Myeloid leukemia (AML)	2
Wilms tumor	2
Renal cell carcinoma	1
Time off therapy (months)	36 (12-116)
Cumulative anthracycline dose, mg/m^2	240 (100-650)

The left ventricular morphological features and systolic functions determined by M-mode echocardiographic examination were similar in childhood cancer survivors and controls (p>0.005) (Table 3). Controls had higher all-day average systolic blood pressure value compared to cancer survivors (107.57±7.39 vs 111.88±7.56, p=0.029). However, the all-day average systolic blood pressure load and central systolic blood pressure were not significantly different between the two groups (23.57±20.2 vs 30.24±18.1, p=0.188, 96.36±6.63 vs 98.84±6.54, p=0.151). Average PWV and Aug@75 values were were not significantly different between childhood cancer survivors and controls (4.4 (4.1-5.2) vs 4.4 (4.1-5.1), p=0.379, 20.81±6.4 vs 21.56±6.46, p=0.655) (Table 4). When cancer survivors were divided into subgroups by age, cancer survivors older than 15 years had similar PWV as controls less than 15 years old (4.68±0.47 vs 4.7±0.29, p=0.639).

Table 3. Comprasion of echocardiographic measurments.

Measurments	Patients (n=38)	Controls (n=25)	P values
IVSDd, mm	7 (4-11.7)	6.5 (4.3-10)	0.386
LVEDd, mm	42.70±4.72	42.33±4.95	0.768
LVPWd, mm	6.27±1.45	6.82±1.19	0.120
LVMI, gr/m^2	63.82±15.03	65.2±14.72	0.721
EF, %	69.94±5.89	69.94±6.36	0.634

EF; ejection fraction, IVSDd; Interventricular septum diameter at end-diastol, LVEDd; left ventricular end-diastolic diameter, LVPWd;left ventricular posterior wall thicness at end-diastol, LVMI; left ventricular mass index.

Table 4. Comprasion of blood pressure and arterial stiffness measurments.

Measurments	Patients (n=38)	Controls (n=25)	P values
24-h average SBP, mmHg	107.57±7.39	111.88±7.56	**0.029**
24-h average DBP, mmHg	63.36±5.41	64.2±3.77	0.507
24-h average cSBP, mmHg	96.36±6.63	98.84±6.54	0.151
24-h average cDBP, mmHg	65 (53-76)	66 (60-74)	0.382
PWV, m/s	4.4 (4.1-5.2)	4.4 (4.1-5.1)	0.379
Aug@75, %	20.81±6.4	21.56±6.46	0.655
24-h SBP load	23.57±20.2	30.24±18.1	0.188
Diurnal systolic variation, %	9.4±5.53	7.77±6.01	0.258

Aug@75; augmentation index, cDBP; central diastolic blood pressure, cSBP; central systolic blood pressure, DBP; diastolic blood pressure, PWV; pulse wave velocity, SBP; systolic blood pressure

The time after chemotherapy completed was negative correlated with shortening fraction and positive correlated with central systolic blood pressure (r=-0.339, p=0.037, r=0.338, p=0.038, respectively).

4. Discussion

According to the current study, left ventricular systolic functions of patients who were received anthracycline for childhood cancer, evaluated at least one year after the end of treatment, were similar with their healthy peers. Central systolic blood pressure and pulse wave velocity examined for the level of arterial stiffness were also not significantly different from their healthy peers. However, cancer survivors, all of whom were normotensive, had lower peripheral systolic blood pressures compared to healthy children.

Childhood cancer survivors have a significantly increased risk of cardiovascular morbidity and mortality (14). Thus, the risk of death from cardiovascular disease in childhood cancer survivors is seven times higher than in the general population (15). Having anthracycline-containing

chemotherapy at an early age further increases this risk (16). Therefore, the screening guidelines of Children's Oncology Group recommended regularly echocardiographic evaluation for children exposed to anthracyclines or radiotherapy to detect early cardiac abnormalities that might be treated (17,18). In the study, left ventricular ejection fraction and shortening fraction were normal in childhood cancer survivors and there was no patient with evident myocardial dysfunction. One of the reasons for the lack of myocardial dysfunction was might be the average cumulative anthracycline dose which was less than 300 mg/m2. However, even children who have received low cumulative doses are known to be at high risk for long-term cardiotoxicity (19). Hence, there may be subclinical findings that cannot be detected by conventional echocardiography methods in childhood, while prominent myocardial systolic dysfunction with a significant decrease in left ventricular EF is diagnosed in long term of life. In addition, the negative relationship between the time remaining after the completion of chemotherapy and systolic functions also emphasizes the increased risk of cardiovascular damage over time.

Decrease in left ventricular mass and wall thickness, which is a precursor of significant systolic dysfunction, is also one of the findings that can be detected in the long-term follow-up of childhood cancer survivors (20). The absence of a decrease in left ventricular wall thickness and mass in childhood cancer survivors compared to controls, may support that morphological impairment in these patients is not a common finding in childhood, just like apparent myocardial dysfunction. In addition, determination of arterial stiffness and central blood pressure values at expected levels in our patients may suggested that there was no increase in central vascular resistance that may lead load dependent myocardial remodeling. Moreover, our finding that childhood cancer survivors had lower peripheral systolic blood pressure values than healthy controls is inconsistent with the literature. Indeed, high peripheral SBP and (pre) hypertension were defined as the late complications of cancer treatment regimens (21). One of the most conceivable explanation for our finding might be the sedentary lifestyle and lower physical activity levels of cancer survivors compared to their healthy peers. Limitations in motor ability due to drug neurotoxicity and developmental delay during long periods of hospital admission may lead to lower physical activity in childhood cancer survivors (22,23). Therefore, sedentary lifestyle habits may have tended to lower 24-hour blood pressure values compared to their more physically active peers. Similar with our results, Nováková et al. were also reported the lower values of systolic blood pressure in children, adolescents, and young adults previously treated with anthracyclines compared to healthy controls of the same age. Moreover, they stated that the age-dependent blood-pressure increase, which was present in healthy adolescents, was not found in cancer survivors (24). Impairment of the sympathetic nervous system caused by anthracycline toxicity, which was reported previously, may lead the lower blood pressure in CCSs (25).

The another issue that is known to be closely associated with long-term mortality in childhood cancer survivors and recommended to be taken into consideration in the follow-up of these patients is vascular damage. Although there are studies on vascular damage in cancer survivors using different methods for evaluation, any method has not yet been included in the guidelines as the standard recommended method. Therefore, the need for defining the most appropriate approach to early detection of anthracyclines-associated vascular damage is an important issue. Pulse wave analysis is a method that allows simple, painless and non-invasive detection of increased arterial stiffness, which is an important finding of vascular damage (26). In the present study, there was no increase in pulse wave velocities and therefore in arterial stiffness, according to the results of the oscillometric pulse wave analysis of the patients. The clearly defined endothelial damage, which is related to anthracyclines in cancer survivors, is closely related to age. Therefore, these patients should be followed for lifetime in terms of cardiovascular toxicity. Furthermore, another treatment modality associated with vascular damage in cancer survivors is radiotherapy (27,28). None

of the childhood cancer survivors included in the study were received radiotherapy, hence this might have been resulted with less vascular damage.

Limitations

The main limitations of our study is the small sample size and lack of long-term follow-up duration. Long-term follow-up of the patients, including their adulthood, will allow the detection of expected vascular damage and myocardial remodeling findings. This may had resulted in the absence of patients with a diagnosis of cardiomyopathy in the cohort of the study. The use of conventional echocardiography to examine cardiotoxicity may be inadequate in detecting findings of subtle cardiotoxicity. These subtle myocardial abnormalities might be demonstrated with further imaging methods such as tissue Doppler imaging, strain echocardiography, and cardiac magnetic resonance imaging. The strength of this study is; it is one of the few studies which arterial stiffness of cancer survivors was assessed by oscillometric pulse wave analysis (29).

5. Conclusion

The results of the present study show that there is no sign of marked deterioration in left ventricular morphology and systolic functions in patients who received anthracycline without radiotherapy due to childhood cancer and who have passed at least one year after the last dose of chemotherapy. According to 24-hour ambulatory blood pressure monitoring and oscillometric pulse wave analysis of these patients, mean systolic blood pressure was not elevated, pulse wave velocity and central blood pressure values were similar to healthy peers, and arterial stiffness was not increased. Longer follow-up duration and advanced imaging modalities may be required for determination of subclinical cardiovascular toxicity signs.

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Research Article / Araştırma Makalesi

Bone Marrow Examinations in 85 Years or Older Geriatric Patients: Indications, Morbidity and Diagnosis.

Seksenbeş Yaş ve Üzerindeki İleri Yaşlı Hastalarda Kemik İliği Değerlendirilmesi: Endikasyonlar, Morbidite ve Tanı

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Abstract

As a result of the population aging, the incidence of both hematologic and non-hematologic diseases of elderly gets higher, requiring bone marrow (BM) aspirations and biopsies be implemented also in the geriatric patients. Our aim in this study is to address BM examination in the geriatric patients aged 85 and over, describing its indications and morbidity and discussing the established diagnoses and outcomes of applied therapies based on BM examinations in comparison to the available literature which is actually limited in number particularly in this patient group. We have retrospectively reviewed the BM aspiration/biopsy results of 114 patients aged ≥ 85 years who were followed-up by hematology department of a university hospital from 2010 to 2020. The patients were selected through the internal data handling system of the hospital using the entry codes corresponding to BM aspiration and biopsy and those at the age of 85 or older were identified. Demographic features, primary diagnosis, any comorbidities, complete blood count (CBC) details, erythrocyte sedimentation rate (ESR), red blood cell indices, C-reactive protein (CRP), serum ferritin, vitamin B12, and folic acid levels, any abnormal results in serum biochemistry testing, the indication(s) for and the result(s) from BM aspiration/biopsy, and the treatments applied based on those result(s) were recorded for each patient as well as the rates of and reasons for mortality. In our cohort of 114 patients with a mean age of 86.3±1.7 (85-93) years, 64.9% (n=74) were males. None of the patients experienced any serious complication during BM aspiration and biopsy. First three indications in our cohort for BM aspiration/biopsy in decreasing order of frequency were cytopenia in 48.2% (n=55), anemia + elevated ESR in 18.4% (n=21), and leukocytosis + anemia + thrombocytopenia in 15.8% (n=18). BM aspiration/biopsy results gave rise to a pathologic or hematologic diagnosis in 85.9% (n=98) and 78.9% (n=90) of patients, respectively. Most frequent hematologic malignancies were myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and multiple myeloma (MM). Kaplan-Meier analysis revealed hemoglobin (Hb) and LDH levels as prognostic factors with an impact on mortality. Prognostic factors with an impact on mortality based on multivariate stepwise Cox regression analysis, on the other hand, were uric (p= 0.018, hazard ratio (HR)= 1.134, 95% confidence interval (CI) = 1.022-1.258), LDH (p=0.092, HR=1.001, 95% CI= 1.000-1.002), and platelet levels (p=0.007, HR=1.000, 95% CI=1.000-1.000). BM examination should definitely be performed in patients aged ≥ 85 years, particularly in the event of cytopenia, unexplained anemia, and elevated ESR both for diagnostic purposes and to prolong life expectancy through administration of modified therapies depending on the performance status. In such patients uric acid, LDH and platelet levels should be closely followed-up as independent prognostic variables which effect mortality.

Keywords: hematology, geriatrics, bone marrow examination, cytopenia

Özet

Yaşlı nüfustaki artışla birlikte, yaşlı nüfusta görülen hematolojik ya da hematolojik dışı hastalıkların insidansında da bir artış gözlenmekte ve geriatrik hasta grubunda da kemik iliği aspirasyon ve biyopsi işlemi endikasyonu gerekli hale gelmektedir Çalışmamızın amacı, 85 yaş ve üzerindeki geriatrik hastalarda kemik iliği (Kİ) değerlendirme işleminin endikasyonlarını tanımlamak, morbiditesini ortaya koymak ve işlem sonucunda elde edilen tanıların ve uygulanan tedavi sonuçlarının özellikle geriatrik yaştaki hasta grubunda yapılmış az sayıdaki diğer çalışmalarla birlikte karşılaştırarak literatüre katkı sağlamaktır. 2010-2020 yılları arasında Üniversite hastanesi hematoloji bölümünde takipleri ve Kİ aspirasyon/biyopsisi yapılmış olan 85 yaş ve üstü olan 114 hastanın sonuçları retrospektif olarak değerlendirildi. Hastalar hastanenin bilgi işlem servisinden Kİ aspirasyon ve biyopsi giriş kodları kullanılarak ve yaşları 85 yaş ve üzeri olacak şekilde tespit edildi. Hastaları demografik özellikleri, primer tanıları, komorbiditeleri, ayrıntılı hemogram sonuçları, eritrosit sedimentasyon hızı (ESH), eritrosit indeksleri, C- reaktif protein (CRP), serum ferritin,vitamin B12, folik asit düzeyleri, anormal serum biyokimya sonuçları, kemik iliği aspirasyon/biyopsi endikasyonları, sonuçları ve sonuçlarda saptanan hematolojik hastalık için kullanılan tedaviler, mortalite oranları ve nedenleri kaydedildi. 114 hastanın %64.9'u (n=74) erkek, ortalama yaşları 86.3±1,7 (85-93) yıl idi. Hiçbir hastada kemik iliği aspirasyon ve biyopsi işlemi sırasında ciddi bir komplikasyon gelişmedi. Kemik iliği aspirasyon/biyopsi endikasyonları ilk 3 sırada; %48.2'sinde (n=55) sitopeni, %18.4'ünde (n=21) anemi+eritrosit sedimentasyon hızı yüksekliği, %15.8'inde (n=18) lökositoz+anemi+trombositopeni idi. 114 hastanın %85.9'unun (n=98) kemik iliği aspirasyon/biyopsi sonucu patolojik saptandı. %78.9'unda (n=90) ise hematolojik bir tanı saptandı. En sık saptanan hematolojik maligniteler myelodisplastik sendrom (MDS), akut myeloid lösemi (AML) ve multiple myeloma (MM) idi. Multivariate Stepwise Cox regresyon analizine göre mortalite üzerine etkili prognostik faktörler; ürik asit (p= 0.018, HR= 1.134 95% CI: 1.022-1.258), laktat dehidrogenaz (LDH) düzeyleri (p=0.092, HR= 1.001, 95% CI: 1.000-1.002), trombosit düzeyleri (p=0.007, HR= 1.000, 95% CI: 1.000-1.000) idi. 85 yaş ve üstü yaşlı hastalarda özellikle sitopeni ve açıklanamayan anemi ve ESH yüksekliği varlığında, tanı koyabilmek ve performans durumuna göre modifiye tedaviler verilerek yaşam süresini uzatmak için kemik iliği değerlendirmesi mutlaka yapılmalıdır. Bu hastalarda ürik asit, LDH ve trombosit düzeyleri mortalite üzerine etkili bağımsız birer prognostik değişken olarak takipte yerini almalıdır

Anahtar Kelimeler: Çocuk, karaciğer nakli, canlı aşılama

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1. Introduction

Bone marrow (BM) examination is an essential investigation method for the diagnosis and treatment of various blood and BM disorders [1,2]. This invasive procedure is in use to diagnose various disorders, whether hematologic or not, across patients of all age groups. Although this method does not have any significant side effects, it is invasive and may cause anxiety in patients [3]. BM examination has a number of indications for which several practical guidelines are available. BM examination is recommended in cases of unexplained anemia, abnormal red blood cell indices, cytopenia(s), cytosis(es), abnormal blood smear morphology suggesting the presence of a BM pathology, suspected BM metastasis, and unexplained organomegaly, and for the purpose of diagnosis, staging and follow-up of malignant hematologic diseases [1]. With the increase in the elderly population, an increase is observed in the incidence of hematological or non-hematological diseases in the elderly population, and the indication for bone marrow aspiration and biopsy procedure becomes necessary in the geriatric patient group [4]. There is a limited number of published studies on BM aspiration and biopsy examination conducted solely in geriatric age group [4-6].

Our aim here is to identify BM examination in the geriatric patients aged 85 and over by describing its indications and morbidity and by discussing the established diagnoses and outcomes of applied therapies based on BM examinations in comparison to the available literature which is actually limited in number particularly in this patient group.

2. Materials and Methods

Patient selection

This study included 114 patients who were followed-up by hematology department of a university hospital from January 2010 to January 2020 and underwent BM aspiration/biopsy at the age of ≥ 85 years. The patients were selected through the internal data handling system of the hospital using the entry codes corresponding to BM aspiration and biopsy and those at the age of 85 or older were identified. Patient results were obtained retrospectively from the patient files or the digital records. Age, gender, primary diagnosis, names of any comorbidities, complete blood count (CBC) details, erythrocyte sedimentation rate (ESR), red blood cell indices, C-reactive protein (CRP), serum ferritin, vitamin B12, and folic acid levels, any abnormal results in serum biochemistry testing, serum immunoglobulin levels and serum protein electrophoresis results, if any, organomegaly status (hepatomegaly, splenomegaly), mortality, if any, and its cause, overall survival (OS) following the BM examination, and the indication(s) for and the result(s) from BM aspiration/biopsy, and the treatments given for the hematologic disease indicated by those result(s) were recorded for each patient. Results of cytogenetic testing were not included into this study.

Definition of cytopenia

A count of hemoglobin <13g/dL in men and hemoglobin <12g/dL in women was accepted as anemia, a leukocyte count of<4000/mm3 was accepted as leucopenia, absolute neutrophil count of <1500/mm3 was accepted as neutropenia, and a platelet count of <100.000/mm3 is accepted as thrombocytopenia. The presence of any one of these values was considered as meeting the criterion for cytopenia.

BM aspiration and biopsy examination

BM aspirates and biopsies were taken from posterior superior iliac spine in accordance with ICSH guidelines [1]. The BM smear preparation was evaluated by experienced hematologists. The BM smear preparation viewed under low power magnification (x10) to determine the number and cellularity of particles, the number of megakaryocytes, and to scan for clumps of abnormal cells incidence. The details of the BM smear at the back of the particles were evaluated at higher magnification (ie, x40, x100). In the diagnosis of hematologic diseases, BM aspiration was evaluated as well as flow cytometric analysis in appropriate patients.

The study was approved by Eskişehir Osmangazi University Ethics Committee in April 2020, with Protocol Number 25403353-0.50.99-E.51579.

Statistical Analysis

Continuous data were depicted as mean ± standard deviation, median (Q1; Q3), while categorical data were depicted as percentage (%).

Shapiro Wilk test was used to compare the conformity of the data to normal distribution. Independent sample t test analysis was used to compare the groups with normal distribution when there were two groups. For the comparison of groups that do not have a normal distribution, Mann-Whitney U test was used. In the analysis of cross tables, Pearson Chi-square, Pearson Exact Chi-square, Yate's Chi-square, Fisher's Exact Chi-square analyses were applied. Cox regression method with stepwise analysis was used to identify the prognostic variables effective on survival. Kaplan- Meier test was applied to compare survivals of two groups (with Log-rank test to assess significant of difference). P value ≤ 0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program.

3. Results

During the time period of 2010-2020, 114 patients underwent BM examination at an age of 85 years or above. Mean age of cohort at the time of procedure was 86.3±1.7 (85-93) years and was consisting of 35.1% (n=40) females and 64.9% (n=74) males. (Demographic characteristic and laboratory results of patients are shown in table 1). A previous disease was known in 85.9% (n=98) of patients, whereas 14% (n=16) had no previously known disease. When ranked by decreasing frequency, first 5 primary diagnoses were diabetes mellitus (DM) in 14.9% (n=17), chronic kidney disease (CKD) in 15.3% (n=15), hypertension (HT) in 13.2% (n=13), coronary artery disease (CAD) in 8.1% (n=8), and chronic obstructive pulmonary disease (COPD) in 7.1% (n=7) (Rates of primary diseases in patients who had undergone BM examination are listed in table 2).

Table 1. Demographics and laboratory features of 114 patients who were underwent bone marrow examination

	Whole group
n	114
Age, mean±SD,(min-max) years	86.3±1.7 (85-93)
Sex (F/M), n	40/74
Laboratory during BM examination, mean±SD, (min-max)	
Hb level, g/dL	9.5±2.4 (3.3-16.5)
MCV level,/fL	90.71±9.5 (65.6-125)
WBC level,/mm^3	23043.8±37801.3 (270-243080)
ANC level,/mm^3	10979.6±19737.5 (0-111000)
ALC level,/mm^3	5475.2±12260.3 (100-73700)
AMC level,/mm^3	5778.4±20224.7 (0-181750)
AEC level,/mm^3	442.6±3243 (0-32800)
PLT level,/mm^3	153000±244132.9 (3000-2200000)
MPV level,/fL	9.03±1.56 (5.8-11.9)
ESR level,mm/h	61.4±41.4 (2-148)
CRP level,mg/dl	16.8±35.7 (0.32-227.2)
Ferritin level,ng/ml	414.2±528 (20-3734)
Vitamin B12 level,pg/ml	751.9±624.3 (55-2000)
Folic acit level, ng/ml	7.85±5.25 (1.53-20)
BUN level,mg/dl	34.9±25.3 (10.4-181.6)
Cr level,mg/dl	1.74±1.58 (0.49-11.23)
LDH level,U/L	674.8±761.9 (163-5774)
Uric acit level,mg/dl	7.1±3.2 (1.9-21)
IgG level, mg/dl	1386.31±835.7 (153-4160)
IgA level, mg/dl	559.8±1166.6 (17-6120)
IgM level, mg/dl	481.6±1619 (15.6-7810)
Deaths n, %	86, 75.4%

Hb; hemoglobin, MCV; mean corpuscular volume, WBC; White blood cell, ANC; absolute neutrophil count, ALC; absolute lymphocyte count, AMC; absolute monocyte count, AEC; absolute eosinophil count, PLT; platelet, MPV; mean platelet volume, ESR; erythrocyte sedimentation rate, CRP; c-reactive protein, BUN; blood urea nitrogen, Cr; creatinine, LDH; lactate dehyrdogenase, Ig; immunoglobulin

Table 2. Distribution of 114 patients with bone marrow examination according to primary disease diagnosis.

Disease	n=114
Primary diseases, n (%)	98 (85.9%)
Diabetes mellitus	17 (17.3%)
Chronic renal failure	15 (15.3%)
Hypertension	13 (13.2%)
Coronary artery disease	8 (8.1%)
Chronic obstructive pulmonary disease	7 (7.1%)
Colon cancer	3 (3.1%)
Benign prostatic hypertrophy	3 (3.1%)
Cerebrovascular disease	3 (3.1%)
Prostate cancer	3 (3.1%)
Heart failure	2 (2%)
Rheumatoid arthritis	2 (2%)
Psoriasis	2 (2%)
Non-Hodkgin lymphoma	2 (2%)
Stomach cancer	2 (2%)
Other causes	16 (16.3%)

Other causes; over cancer, myelodysplastic syndrome, malignant melanom, bladder cancer, dementia, osteoporosis, osteoarthritis, polycythemia vera, emphysem, parkinson, chronic myeloid leukemia, cardiomyopathy, atypical hemolytic uremic syndrome

Of 114 patients, 86.8% (n=99) had anemia. We could access the mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values for 95% (n=94) of 99 anemic patients. When morphology of anemia was investigated in those 94 patients, 75.5% (n=71) had normochromic, normocytic anemia; 9.6% (n=9) had hypochromic, microcytic anemia; and 14.8% (n=14) had macrocytic anemia.

Leukocyte measurements were available in 97.4% (n=111) of 114 patients. Accordingly, 36.9% (n=41) had leukocytosis and 26.1% (n=29) had leukopenia. We could reach absolute neutrophile and platelet counts of 98.2% (n=112) of patients which demonstrated 20.5% (n=23) had neutropenia and 67.9% (n=76) had thrombocytopenia. Absolute monocyte counts were retrieved in 88.6% (n=101) of patients. Monocytosis was detected in 30.7% (n=31) of patients. LDH levels were accessed in 86.8% (n=99) of our cohort , of whom 81.8% (n=81) had increased LDH.

Cytopenia, in at least one lineage, was detected in 93.9% (n=107) of our 114 patients.

Among the 48.2% (n=55) patients whose indication for BM aspiration/biopsy was cytopenia, subtype was determined as bicytopenia, pancytopenia, and isolated cytopenia in 27.2% (n=15), 49% (n=27), and 23.6% (n=13), respectively. BM findings were indicating dysplasia in 48.2% (n=55) of patients.

At least one comorbid disease was determined in 83.3% (n=95) of our patients who were aged 85 years or older. Most common comorbidities and their respective percentages were: HT: 53.6% (n=51), DM: 34.7% (n=33), CAD: 29.5% (n=28), CKD: 20% (n=19), and COPD: 16.8% (n=16).

Of our patients, 42.1% (n=48) were on antiaggregants and 42.1% (n=48) were on anticoagulants (low molecular weight heparin, warfarin, or novel oral anticoagulant). None

of the patients experienced any serious complication during BM aspiration and biopsy.

Mean size of BM biopsy collected from the patients were 1.08±0.45 (0.3-2.3) cm. BM cellularity, on average, was 51.2%±25.7% (0-100).

As it was indicated, serum immunoglobulin level measurement and serum protein/immunofixation electrophoresis was conducted in 32 patients, results of which revealed monoclonal gammopathy in 59.4% (n=19) and polyclonal gammopathy 25% (n=8).

In our study cohort, BM aspiration/biopsy results gave rise to a pathologic or hematologic diagnosis in 85.9% (n=98) and 78.9% (n=90) of patients, respectively. A hematologic diagnosis was established in 90 patients, of which 88.8% (n=80) were a malign hematologic diagnosis. When a hematologic diagnosis was made, 96.6% (n=87) of the patients received a treatment for that hematologic diagnosis and 41.3% (n=36) received chemotherapy treatment.

Indications for BM aspiration/biopsy

The breakdown of BM aspiration/biopsy indications by number of patients was as follows: cytopenia in 48.2% (n=55), anemia+elevated ESR in 18.4% (n=21), leukocytosis+ anemia+thrombocytopenia in 15.8% (n=18), anemia+lymphocytosis+thrombocytopenia in 2.6% (n=3), anemia+leukocytosis+elevated ESR in another 2.6% (n=3), anemia+proteinuria+elevated ESR in yet another 2.6% (n=3), anemia+monoclonal gammopathy in 1.8% (n=2), lymphocytosis in another 1.8% (n=2), and other causes in 6.1% (n= 7) (Indications for BM examination are given in table 3).

Table 3. Indications for bone marrow examination of 114 patients

BM examination causes	n(%)
Cytopenia	55(48.2%)
Pancytopenia	27(49%)
Bicytopenia	15(27.2%)
Anemia and thrombocytopenia	13(86.6%)
Anemia and neutropenia	2(15.4%)
Isolated cytopenia	13(23.6%)
Isoletaed neutropenia	3(23.1%)
Isoletaed thrombocytopenia	7(53.8%)
Isolated leucopenia	1(7.6%)
Isolated anemia	2(15.4%)
Anemia and high ESR levels	21(18.4.%)
Leucocytosis and anemia and thrombocytopenia	18(15.8%)
Anemia and lymphocytosis and thrombocytopenia	3(2.6%)
Anemia and leucocytosis and high ESR levels	3(2.6%)
Anemia and proteinuria and high ESR levels	3(2.6%)
Anemia and monoclonal gammapathy	2(1.8%)
Lymphocytosis	2(1.8%)
Leucocytosis and thrombocytopenia	1(0.9%)
Follow-up staging of known lymphoma	1(0.9%)
Anemia and high ESR levels and thrombocytopenia	1(0.9%)
High ESR levels and pancytopenia	1(0.9%)
Suspicion of plasma cell myeloma after known plasmacytoma	1(0.9%)
Anemia and leucocytosis and thrombocytosis	1(0.9%)
Eosinophilia	1(0.9%)

BM; bone marrow, ESR; erythrocyte sedimentation rate

Pre-diagnosis prior to BM aspiration/biopsy

Pre-diagnosis prior to BM aspiration and biopsy were as follows: multiple myeloma (MM)/plasma cell dyscrasia in 21.9% (n=25), myelodysplastic syndrome (MDS) in 36.8% (n=42), acute leukemia in 16.7% (n=19), chronic lymphocytic leukemia (CLL) in 5.3% (n=6), immune thrombocytopenia (ITP) in 5.3% (n=6), involvement of lymphoma in 2.6% (n=3), chronic myelomonocytic leukemia (CMML) in 2.6% (n=3), Waldenstrom's macroglobulinemia (WM) in 0.9% (n=1), chronic myeloid leukemia (CML) in 0.9% (n=1), hairy cell leukemia (HCL) in 0.9% (n=1), amyloidosis in 0.9% (n=1), BM metastasis of colon cancer in 0.9% (n=1), essential thrombocytosis (ET) in 0.9% (n=1), post–polycythemia vera myelofibrosis (post-PV MF) in 0.9% (n=1), BM metastasis of stomach cancer in 0.9% (n=1), methotrexate-induced BM suppression in 0.9% (n=1), and hypereosinophilic syndrome (HES) in 0.9% (n=1).

Results of BM aspiration/biopsy

In our study cohort, BM aspiration/biopsy results gave rise to a pathologic or hematologic diagnosis in 85.9% (n=98) and 78.9% (n=90) of patients, respectively. A hematologic diagnosis was established in 90 patients, of which 88.8% (n=80) were a malign hematologic diagnosis. The results of BM examinations of our patients were as follows: MDS in 19.3% (n=22), acute myeloid leukemia (AML) in %14.9 (n=17), normal in 14% (n=16), MM in 10.5% (n=12), ITP in 7% (n=8), MDS refractory anemia with excess blasts (RAEB) type-2 in 5.3% (n=6), reactive plasmacytosis in 5.3% (n=6), CLL in 3.5% (n=4), MDS-RAEB-type 1 in 2.6% (n=3), CMML in 2.6% (n=3), WM in 1.8% (n=2), marginal zone lymphoma (MZL) in 1.8% (n=2), B-cell non-Hodgkin's lymphoma (NHL) in 1.8% (n=2), methotrexate-induced BM hypocellularity in 1.8% (n=2), CML in 0.9% (n=1), B-cell acute lymphoblastic leukemia (ALL) in 0.9% (n=1), HCL in 0.9% (n=1), ET in 0.9% (n=1), post-PV MF in 0.9% (n=1), monoclonal gammopathy of undetermined significance (MGUS) in 0.9% (n=1), erythroid hyperplasia (EH) in 0.9% (n=1), AA amyloidosis in 0.9% (n=1), and HES in %0.9 (n=1). (Characteristics of 80 patients who were diagnosed with a malignant hematologic pathology based on the evaluation of BM aspiration/biopsy are given in table 4).

Mortality rates and prognostic factors

Starting from the day BM aspiration/biopsy was collected from the patients, median OS time was 180 (range 28.2-547.5) days. During the course of study, 24.6% (n=28) of patients survived, whereas 75.4% (n=86) died. We have identified the reason for mortality was sepsis in 18.6% (n=16), sepsis+pulmonary infection in 15.1% (n=13), progression of primary disease in 5.81% (n=5), cerebrovascular disease (CVD) in 4.65% (n=4), intracranial hemorrhage in 2.32% (n=2), intracranial hemorrhage+pneumonia+disseminated intravascular coagulation (DIC) in 1.16% (n=1), femoral fracture+pulmonary embolism+CVD in 1.16% (n=1), ovarian cancer+multi-organ failure in 1.16% (n=1), progression of AML+atrial fibrillation (AF)+ pneumonia in 1.16% (n=1), sepsis+AF in 1.16% (n=1), massive gastrointestinal (GI) bleeding in 1.16% (n=1), myocardial infarction (MI)+urosepsis in 1.16% (n=1), GI bleeding+intracranial hemorrhage in 1.16% (n=1), acute cerebral infarction+cholangitis+sepsis in 1.16% (n=1), catheter infection+urosepsis in 1.16% (n=1), pancreatitis+GI bleeding in 1.16% (n=1), leukostasis+pneumonia in 1.16% (n=1), pneumonia+heart failure in 1.16% (n=1), emphysema+pneumonia in 1.16% (n=1), MI in 1.16% (n=1), heart failure+acute pulmonary edema+pneumonia+acute kidney failure in 1.16% (n=1), and no reason could be identified in 34.8% (n=30) of our patients.

Mortality was significantly higher among those with an elevated LDH level compared to the patients with lower LDH levels ($p<0.01$).

Median duration of OS was 120 (range 45.3-194.6) days in higher (abnormal) LDH group, while respective duration was 480 (range 164.4-795.5) days in lower (normal) LDH group, making a statistically significant difference ($p=0.027$) (Figure 1.A).

We also compared survival of the patients by the most common pathological BM examination results (MDS, AML, and MM). The shortest OS was in AML [median 30 (range 21.3-38.6) days] patients, the longest OS was in MDS subgroup except for elevated blast [median 360 (0-756) days] and MM subgroup had a median OS of 90 (range 0-267.6) days ($p<0.0001$) (Figure 1.B).

Table 4. Characteristics of 80 patients with malignant hematological pathology as a result of bone marrow aspiration/biopsy.

Malign hematologic disease	Indications for bone marrow examination	Preliminary diagnosis	Outcome	Treatment
MDS n=22	21 cytopenia, 1 leucocytosis and anemia and thrombocytopenia	20 MDS 2 ITP	7 alive 15 dead	Transfusion, G-CSF, IVIG, methylprednisolone, danazol, erythropoietin
MDS-RAEB-type 1 n=3	3 cytopenia	3 MDS	1 alive 2 dead	Transfusion, iron chelation therapy, 5-azacytidine
MDS-RAEB-type 2 n=6	6 cytopenia	6 MDS	2 alive 4 dead	Transfusion, iron chelation therapy, 5-azacytidine, IVIG
CMML n=3	2 leucocytosis and anemia and thrombocytopenia 1 anemia and leucocytosis and high ESR levels	3 CMML	3 dead	Transfusion, hydroxyurea, 5-azacytidine, decitabine, etoposide, IVIG
AML n=17	13 leucocytosis and anemia and thrombocytopenia 3 cytopenia 1 leucocytosis and thrombocytopenia	14 Akut leukemia 2 MDS	1 alive 16 dead	Transfusion, leukapheresis, hydroxyurea, 5-azacytidine, subcutaneous cytosine arabinoside, etoposide
B-ALL n=1	Leucocytosis and anemia and thrombocytopenia	Acute leukemia	dead	Transfusion, hydroxyurea, methylprednisolone
MM n=12	5 anemia and high ESR levels 2 anemia and monoclonal gammapathy 1 anemia and lymphocytosis and thrombocytopenia 1 anemia and high ESR levels and thrombocytopenia 1 cytopenia 1 high ESR levels and pancytopenia 1 suspicion of plasma cell myeloma after known plasmacytoma	11 MM 1 CLL	2 alive 10 dead	Transfusion, plasma exchange, bortezomib, dexamethasone, melpahalan, methylprednisolone, radiotherapy, zoledronic acid
WM n=2	1 anemia and high ESR levels 1 cytopenia	1 WM 1 MM/ plasma cell dyscrasia	2 dead	Transfusion, plasma exchange, cyclophosphamide, vincristine, methylprednisolone
MGUS n=1	Anemia and high ESR levels	MM	dead	IVIG
CLL n=4	2 lymphocytosis 1 anemia and high ESR levels 1 anemia and lymphocytosis and thrombocytopenia	3 CLL 1 ITP	2 alive 2 dead	Transfusion, chlorambucil, methylprednisolone
B-cell NHL n=2	1 anemia and lymphocytosis and thrombocytopenia 1 cytopenia	1 CLL 1 Akut leukemia	1 alive 1 dead	Transfusion, rituximab, cyclophosphamide, vincristine, methylprednisolone, G-CSF
MZL n=2	1 anemia and high ESR levels 1 anemia and leucocytosis and high ESR levels	1 CLL 1 MM/ plasma cell dyscrasia	1 alive 1 dead	Transfusion, plasma exchange, methylprednisolone
CML n=1	Leucocytosis and anemia and thrombocytopenia	CML	dead	Hydroxyurea, imatinib
ET n=1	Anemia and leucocytosis and thrombocytosis	ET	dead	Hydroxyurea, acetylsalicylic acid
Post-PV MF n=1	Anemia and leucocytosis and high ESR levels	Post-PV MF	dead	Transfusion, ruxolitinib
HES n=1	Eosinophilia	HES	dead	Hydroxyurea, methylprednisolone
HCL n=1	Cytopenia	HCL	alive	Transfusion, cladribine

MDS; myelodysplastic syndrome, AML; acute myeloid leukemia, MM; multiple myeloma, RAEB; Refractory anemia with excess blasts, CMML;Chronic myelomonocytic leukemia, WM; Waldenstrom macroglobulinemia, NHL; non-Hodkgin lymphoma, MZL; marginal zone lymphoma, ALL; acute lymphoblastic leukemia, CML; chronic myeloid leukemia, HCL; hairy cell leukemia, ET; essential thrombocythemia, Post-PV MF; post–polycythemia vera myelofibrosis, MGUS; monoclonal gammopathy of undetermined significance, HES; hypereosinophilic syndrome, ITP; immune thrombocytopenia, ESR; erythrocyte sedimentation rate, G-CSF; granulocyte colony-stimulating factor, IVIG; intravenous immunoglobulin.

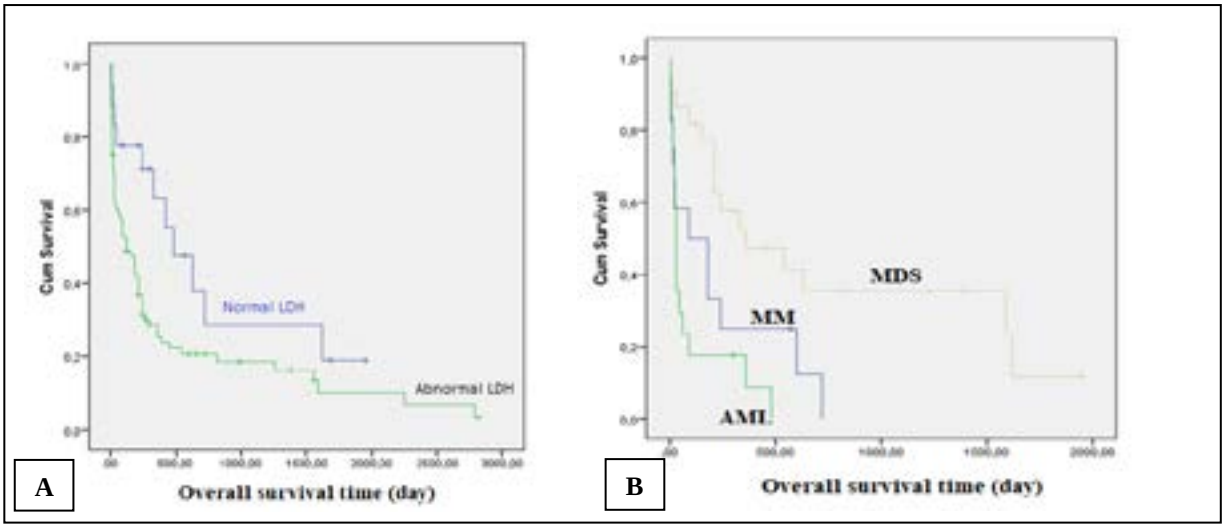

Figure 1. Overall survival curves of the 85 years and older patients based on (A) LDH levels (B) Their diagnosis.

Comparison of LDH levels of the patients with and without a pathological BM aspiration/biopsy result revealed higher LDH levels in those with pathological results, but not to a significant extent (712.1±87.1 vs 467.5±132.2, p>0.05).

Kaplan-Meier analysis identified laboratory parameters Hb and LDH level were prognostic factors effective on mortality (comparison of patients who died and who survived; mean Hb 9.1±2.2 g/dL vs 10.9±2.6 g/dL; median LDH 529 vs 262 IU/L (p=0.002, p<0.0001, respectively).

Multivariate stepwise Cox regression analysis revealed that uric acid, LDH and platelet levels were the prognostic variables that affect mortality (Table 5).

Table 5. Multivariate analysis on overall survival in 85 years and older patients undergoing bone marrow examination

Variables	Hazard ratio (95% CI)	p value
Uric acid levels	1.134 (1.022-1.258)	p= 0.018
LDH levels	1.001 (1.000-1.002)	p=0.092
Platelet levels	1.000 (1.000-1.000)	p=0.007

LDH; lactate dehyrdogenase

4. Discussion

The older the population ages, the higher the incidence of both hematologic and non-hematologic diseases of elderly gets. More than likely, we will be conducting BM aspiration/biopsy more frequently in patients of advanced age as the population gets older. There is a limited number of published studies on BM aspiration and biopsy examination conducted solely in geriatric age group [4,5]. In our study, we evaluated the bone marrow aspiration/biopsy examination process in geriatric patients aged 85 and over.

BM examination has a number of indications. BM examination is recommended in cases of unexplained anemia, abnormal red blood cell indices, presence of cytosis, suspected BM metastasis, and for the purpose of diagnosis, staging and follow-up of malignant hematological diseases [1]. Indications for BM aspiration/biopsy in infants, children as well as young and middle-aged adults may differ from those in elderly. In the general population composed of infants, children, and young and middle-aged adults, most common indication for BM examination is staging of

acute leukemia and lymphoma whereas unexplained cytopenia and anemia stands for the most frequent indications among elderly and extremely elderly [4,5,7]. In the study of Manian E. et al. conducted with patient aged 85 years and older, the most common indications were cytopenia in 36.1% and followed by thrombocytosis or leukocytosis in 14.3% (n=17), Gulati A. et al., on the other hand, stated unexplained anemia ranked at the first place in their cohort composed of ≥ 60 year-old patients [4,5]. Our study recruited 114 patients at the of 85 or above and most common indication for BM aspiration/biopsy were cytopenia taking place in 48.2% (n=55) of our patients followed by anemia+elevated ESR in 18.4% (n=21), and triad of leukocytosis+anemia+thrombocytopenia in 15.8% (n=18). In our study, the most common indication for bone marrow examination was cytopenias, accounting for almost half of the cases. Based on our review of existing literature comparing our results, we had very few elderly patients undergoing BM examination due to thrombocytosis or leukocytosis. Furthermore, the second most common indication in our cohort, namely anemia + elevated ESR, was also not alike the literature.

BM aspiration/biopsy examination is an invasive procedure used to diagnose various hematologic or non-hematologic disorders. A specific malignant hematologic diagnosis was made upon BM aspirations/biopsies in 43% and 43.3% of cases in the studies by Manian E. et al and Gulati A. et al, respectively [4,5]. In our study, 85.9% (n=98) out of 114 patients had a pathology based on their BM aspiration/biopsy results and 70.1% (n=80) were diagnosed with a specific hematologic malignancy. Our study is first of its kind with the highest ratio of specific malignant hematologic diagnosis so far in literature among patients aged 85 and over.

When BM examination is carried out due to the indication of cytopenia, the likelihood to establish a specific diagnosis is quite small in patients of advanced age who are ≥ 85 years old, in whom the highest rates of diagnosis were reported for leukocytosis and thrombocytosis [4]. Manian E. et al have advocated undergoing BM aspiration/biopsy would bring no difference in terms of clinical management or outcomes in majority of elderly patients with cytopenia and therefore suggested cytopenia should be followed-up as long as there is no suspected clonal myeloproliferative disorder [3,4]. On contrary to the literature data, we have achieved quite a high figure of specific diagnosis among our patients ≥ 85 years old who underwent BM examination due to cytopenia, and most frequently diagnosed them with low-risk or high-risk MDS. In line with our results and given its very low morbidity, we consider BM examination should be an integral part of diagnostic workup and treatment management in extremely elderly patients with cytopenia.

Anemia is very common among this patient population and has been recognized as an important cause of morbidity. Anemia may arise from a plethora of reasons in elderly including nutritional insufficiency (most often in forms of megaloblastic and micronormoblastic), chronic inflammation, chronic kidney disease, MDS as well as from an unexplained etiology in many patients [8-10]. In anemic patients of advanced age, BM aspiration/biopsy is a reliable intervention with a complication rate of < 0.05% and thus should be performed to rule out MDS and any other hematologic disorders [3,4]. In our study, anemia+elevated ESR was the second most common cause for BM aspiration/biopsy examination and specific diagnoses of MM, WM, and MZL were established quite frequently in this subgroup. None of the patients in our cohort had experienced any serious complication during BM aspiration/biopsy.

Although rare among children and young adults, the incidences of MDS and chronic myeloproliferative neoplasms (CMPNs) as well as leukemia and lymphoma are known to increase with age [11]. In their study including patients at the age of 85 and above who have underdone BM examination, Manian E. et al reported one third of the newly diagnosed cases were MDS and CMPNs [4], while two thirds of our cases were composed of MDS, AML, and MM. Dissimilar to the literature data, in our patient

cohort of BM examination patients aged ≥ 85 years, AML and MM were diagnosed more often and CMPNs were diagnosed less often.

Due to their performance status, supportive care is preferred over chemotherapy regimens in elderly with malignancies. Our literature search figured out the specific diagnoses in 79 of 119 patients aged ≥ 85 years who experienced BM aspiration/biopsy. Furthermore, we accessed follow-up details of 56.9% (n=45) of whom 44% (n=20, 9 lymphoma, 5 MM, 3 AML, 3 CMPN or MDS) were treated and only 17 were administered a modified or dose-reduced regimens due to poor performance status or drug intolerance. Eventually, all of these treatment were reported as unsuccessful [4]. In our study, on the other hand, a hematologic diagnosis was made for 90 patients leading to prescription of a treatment for that hematologic diagnosis in 96.6% (n=87) of the patients and 41.3% (n=36) of treatment receivers were given chemotherapy (Details are given in table 4). Even if a hematologic malignancy develops in extremely elderly patients, it is still possible to prolong their OS by applying dose-reduction or modified treatment regimens along with supportive care taking their performance status into account.

None of the former BM aspiration/biopsy studies conducted on elderly population so far has evaluated the OS, rates and causes of mortality, or the prognostic factors which affect mortality [4,5]. A distinct aspect of our study is we have also provided mortality rates, causes of mortality, and the prognostic variables with an impact on mortality in our patient group. Our analysis showed 24.6% (n=28) of patients survived, whereas 75.4% (n=86) died. Most frequent reason of mortality was sepsis. Hb and LDH levels were identified as prognostic variables which affect mortality. LDH, uric acid, and platelet levels were each an independent prognostic variable effective on OS. In the extremely elderly patient group, particularly in patients aged ≥ 85 years, for whom BM aspiration/biopsy is indicated and therefore BM examination is applied, it is likely that Hb, LDH, uric acid, and platelet levels will help clinicians during the follow-up of patients as factors effective on OS and mortality.

The main limitation of this study is its retrospective design. Second, the number of patients is relatively small.

Consequently, BM aspiration/biopsy procedure features out with its low complication rate in patients at the age of ≥ 85 years, as in other age groups. Therefore, clinicians should not avoid diagnostic BM examination in this age group, especially in the event of unexplained cytopenia in combination with elevated ESR, as it offers a high likelihood of specific diagnosis.

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Olgu / Case Report

A Case with Kounis Syndrome After the Administration of Metoclopramide

Metoklopramide Bağlı Gelişen Kounis Sendromu Olgusu

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Abstract

Kounis syndrome is characterized by a symptoms that cause unstable vasospastic or non-vasospastic angina secondary to a hypersensitivity reactions. After identification by Kounis in 1991, this syndrome includes a series of mast cell activation disorders associated with acute coronary syndrome. There are many triggering factors, including reactions to multiple medications, foods such as fish, tomato, fruits, bee stings poison ivy, viper venom, shellfish and coronary stents. We report the case of 71-year-old man with no coronary risk factors or family history of coronary artery disease, who developed Kounis syndrome after the administration of metoclopramide for nausea.

Keywords: Kounis, myocardial infarction, allergy, metoclopramide

Özet

Kounis sendromu, aşırı duyarlılık reaksiyonlarına sekonder kararsız vazospastik veya vazospastik olmayan anjinaya neden olan semptomlarla karakterizedir. Kounis tarafından 1991'de tanımlandıktan sonra bu sendrom, akut koroner sendromla ilişkili bir dizi mast hücresi aktivasyon bozukluğunu içerir. Çoklu ilaçlara verilen reaksiyonlar, balık, domates, meyve, arı sokması zehirli sarmaşık, engerek zehiri, kabuklu deniz ürünleri gibi gıdaları ve koroner stentleri içeren birçok tetikleyici faktör vardır. Olgumuzda, bulantı için metoklopramid uygulandıktan sonra Kounis sendromu gelişen koroner risk faktörü veya aile öyküsünde koroner arter hastalığı bulunmayan 71 yaşında erkek hastayı sunuyoruz.

Anahtar Kelimeler: Kounis, miyokard enfarktüsü, allerji, metoklopramid

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1. Introduction

Kounis syndrome (KS) is defined as the concurrence of acute coronary syndromes (ACS) such as coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with allergic or hypersensitivity or anaphylactic conditions [1]. Chest pain is one of the most frequent complaints in emergency admission. Hence, it is one of the serious life-threatening condition, early diagnosis is very important. KS is not uncommon but is ignored due to the doctor's focus on the main complaint at the time of emergency presentation. This condition, also called allergic angina, may progress to acute myocardial infarction called allergic myocardial infarction [2, 3]. Causes that can elicit KS include many medications, environmental exposure, asthma, idiopathic anaphylaxis, and conditions such as mastocytosis. In the present study, we report the case of 71-year-old man with no coronary risk factors or family history of coronary artery disease and no drug use history, who developed Kounis syndrome after the administration of metoclopramide for nausea and its pathophysiology was described below.

2. Case

A 71-year-old male with a history of allergic disease and hypertension was presented to our emergency department after sudden syncope. Before admission, he was complaining of nausea and vomiting. He presented with a pulse rate 36 beats per minute, sPO2 98% (fiO2 66%), and blood pressure 130/80 mmHg. Due to his confusion state before admission, we take a detailed history one hour after the initial symptoms. From his history, it was revealed that he was taken metoclopramide 10 mg intravenously (i.v.) for nausea. We recorded a 12-lead electrocardiogram (ECG), which showed ST segment elevation in the inferior, anterior and lateral leads and 3. degree AV block (figure 1). Blood tests revealed elevated levels of glucose: 152 mg/dl, creatinine: 1,3 mg/dl, troponin I: 0.05 mg /dl, and CKMB: 1,6 mg/dl.

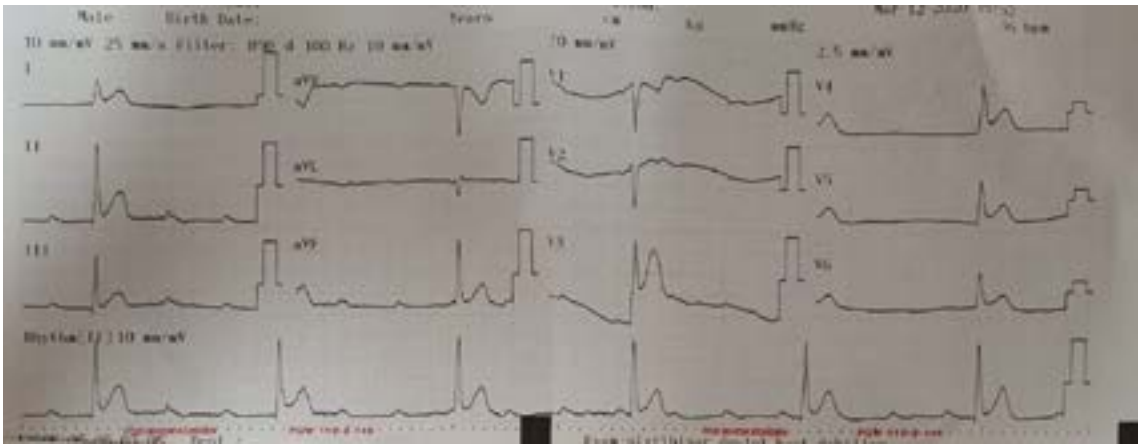

Figure 1. ECG at the time of complaints

Within the first hours of admission, the patient became asymptomatic with normalization of ECG (figure 2). Echocardiography revealed no segmental systolic dysfunction and other abnormalities with a normal physical examination. Patient who does not accept angiography suggestion, was discharged from intensive care unit, 24 hours after the ED admission

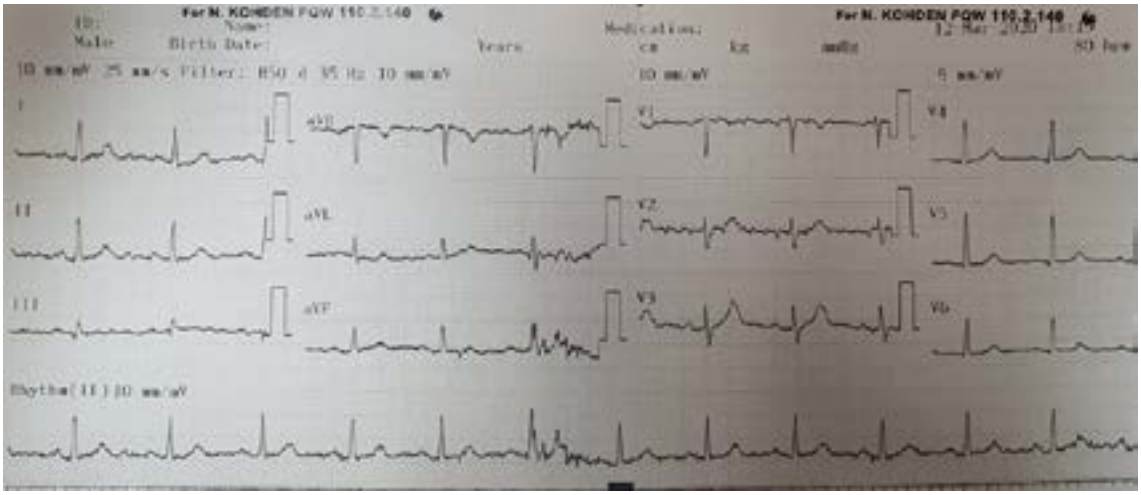

Figure 2. ECG after complaints

3. Discussion

Cardiovascular symptoms and signs associated with allergic, hypersensitivity or anaphylactic reactions began to appear in the medical literature about 70 years ago [4, 5].

KS is classified into 3 variants. Tip 1, includes normal or nearly normal coronary arteries without risk factors for coronary artery disease or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins also without increased in cardiac enzymes such as troponin I. Type II variant includes culprit but quiescent preexisting atheromatous disease in which the acute release of inflammatory mediators may induce either coronary artery spasm or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction. Type III variant includes coronary artery stent thrombosis [1]. Our patient is classified as type I variant. This syndrome is caused by histamine, platelet-activating factors, arachidonic acid products, neutral proteases, and inflammatory mediators such as various cytokines and chemokines released during the allergic process [1]. In recent studies, it has been reported that the effects of Kounis-like syndromes can occur in the mesenteric [6] system and cerebral circulation [7].

KS is not uncommon but has not been frequently reported in the literature. There are many factors that cause KS (table 1) [8]. According to the literature, non-steroidal anti-inflammatory drugs have been reported as one of the most common cause [9]. The incidence of KS was reported as 4.33 cases per 100,000 people [10]. In a study conducted in Turkey, the estimated prevalence of the catheterization laboratory of KS is 0.002 % [11]..

Table 1. Causes associated with Kounis syndrome

Drugs	Conditions	Food	Environmental
Analgesics (aspirine, dipyrone)	Angioedema	Actinidia chinensis	Grass cutting
Anesthetics (etomidate, isoflurane, midazolam,propofol, remifentanil, rocuronium bromide,succinylcholine, suxamethonium, trimethaphan	Bronchial asthma	Canned food (tuna)	Hymenoptera stings
Antibiotics (ampicillin, ampicillin/sulfactam, amoxicillin, amikacin, cefazolin, cefoxitin, cerufoxime, cephradine, cinoxacin, lincomycin, penicillin, sulbactam/cefoperazone, piperacillin/tazobactam,	Churg-Strauss syndrome	Fish	Jellyfish stings

trimethoprimsulfamethoxazole, sulperazon, vancomycin)			
Anticoagulants (heparin, lepirudin)	Exercise-induced anaphylaxis	Fruits	Latex contact
Anti-neoplastics (5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel, vinca alkaloids)	Food allergy	Mushroom poisoning	Millet allergy
Contrast media (Iohexone, loxagate, meglumine diatrizoate, sodium indigotindisulfonate)	Idiopathic anaphylaxis	Shellfish	Poison ivy
Glucocorticoids (betamethasone, hydrocortisone)	Nicotine	Vegetables	Scorpion sting
Nonsteroidal anti-inflammatory drugs (alclofenac, diclofenac, naproxen)	Scombroid syndrome	Tomato salad	Viper venom
Proton pump inhibitors (lansoprazole)	Skin itching		Metals
Thrombolytics (streptokinase, tissue plasminogen activator, urokinase)	Stents (bare metal, drug eluting)		
Others (allopurinol, bupropion, clopidogrel, dextran, enalapril, esmolol, fructose, gelofusin, insulin, iodine, iron, losartan, protamine, tetanus antitoxin, glaphenine, mesalamine)			

Diagnosis of KS is based on clinical symptoms and findings, as well as laboratory, electrocardiographic, echocardiographic and angiographic evidence. The first signs and symptoms of KS in the emergency room are always associated with allergic reactions accompanied by cardiac symptoms. Symptoms observed in this syndrome are chest pain, dyspnea, faintness, malaise, nausea, vomiting, pruritis, skin itching and syncope [8]. Clinical findings are cold extremities, diaphoresis, hypotension, pallor, palpitation, skin rash, sweating and sudden death.

An electrocardiogram is very important in clinical diagnosis. The most common ECG findings are ST-segment elevation, atrial fibrillation, heart block, nodal rhythm, sinus bradycardia, sinus tachycardia, T wave changes, QRS prolongation and ventricular fibrillation [8].

Although it is not infrequent, patients are more often encountered in clinical practice but it is rarely diagnosed and can be easily overlooked by emergency physicians. Many of these findings may accompany allergic symptoms, which helps to make an accurate diagnosis. A high suspect index is very important for diagnosis.

In blood tests, serum tryptase, histamine, cardiac enzymes and cardiac troponins can be especially helpful in diagnosis, early taken of the first blood sample is essentials for the rapid diagnosis [12]. Histamine release from mast cells is fast and short-lived and circulates only 8 minutes after an allergic event, so blood samples should be collected immediately after the onset of chest pain [13]. Cardiac enzymes are valuable in diagnosing cardiac damage. Measurement of cardiac troponins has been recommended in all patients with KS admitted to the emergency department to diagnose and properly manage a potential heart injury in the emergency department [14].

Finally, echocardiography and coronary angiography are required for the diagnosis of cardiac wall abnormalities and identification of coronary anatomy in KS. In diagnosis, dynamic cardiac magnetic resonance imaging (MRI) as well as new techniques such as Thallium-201 single-photon emission computed tomography (SPECT) and 125I-15-3- (R, S) methylpentadinanoic acid (SPECT) can be used to assess cardiac involvement [15, 16].

ACS secondary to allergic reactions can cause morbidity and mortality in these patients. Systemic allergic reactions should be checked early in the treatment. However, the therapeutic management of KS can be difficult because both cardiac and allergic symptoms must be treated together. Drugs

used to treat both conditions can worsen clinics [17]. As in Type 1 variant, only treatment of an allergic event may end symptoms in our patients. The use of i.v. corticosteroids and H1, H2 antihistamines are adequate. Using nitrate as a vasodilator can treat vasospasm due to hypersensitivity. Nitroglycerin can worsens hypotension and tachycardia, which occurs in the anaphylactic reaction therefore oral, sublingual and i.v. nitroglycerin are tolerable if the blood pressure is satisfactory [17].

4. Conclusion

KS is a complex ACS type that requires rapid diagnosis and treatment, so, management in the emergency is a keystone for improvement both morbidity and mortality of this patient population . A detailed history including potential allergen exposure, ECG and cardiac enzymes are mandatory part of the management strategy in all suspected patients for accurate diagnosis and rapid treatment.

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Olgu / Case Report

Congenital Hypofibrinogenemia or Afibrinogenemia?; A Diagnostic Dilemma in Neonatal Period

Konjenital Hipofibrinojenemi veya Afibrinojenemi? Yenidoğan Döneminde Tanısal Bir İkilem

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Abstract

Congenital Afibrinogenemia/Hypofibrinogenemia (OMIM, 202400) (CA/CH) is one of the rare causes of hereditary hemostasis and is inherited in an autosomal-recessive. Spontaneous bleedings are not common unless the fibrinogen level is below 0.7-1 g/L. Congenital afibrinogenemia is characterized with prolonged Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR), Thrombin Time (TT), and very low or unmeasurable fibrinogen levels. Here, we presented a newborn who was initially diagnosed as CH according to fibrinogen level but we confused with genetic examination which revealed a homozygote deletion in the whole FGA gene compatible with CA. Fibrinogen level (<35 mg/dL) of the infant decreased during follow up and the diagnosis of CA became clear. We want to take attention of clinicians to that laboratory findings may not correlate with genotype leading to a diagnostic dilemma in neonatal period,and sometimes diagnostic puzzle completes during follow up.

Keywords: Newborn, Congenital afibrinogenemia/hypofibrinogenemia, Bleeding Diathesis

Özet

Konjenital Afibrinojenemi / Hipofibrinojenemi (OMIM, 202400) (CA / CH), kalıtsal hemostazın nadir nedenlerinden biridir ve otozomal resesif olarak kalıtılır. Fibrinojen seviyesi 0.7-1 g / L'nin altında olmadığı sürece spontan kanamalar yaygın değildir. Konjenital afibrinojenemi, uzamış Protrombin Süresi (PT), aktive Parsiyel Tromboplastin Süresi (aPTT), Uluslararası Normalize Oranı (INR), Trombin Süresi (TT) ve çok düşük veya ölçülemeyen fibrinojen seviyeleri ile karakterizedir. Burada fibrinojen düzeyine göre başlangıçta CH tanısı konmuş ancak genetik analizi CA ile uyumlu tüm FGA geninde homozigot delesyon saptanan bir yenidoğanı sunulmuştur. İzlemde bebeğin fibrinojen düzeyi azalmış ve hatta çok düşük seyretmiştir (<35 mg / dL) ve CA tanısı izlemde netleşmiştir. Laboratuvar bulguları yenidoğan döneminde klinisyenler için yanıltıcı olabilir, sonuçlar genotip ile uyumlu olmayabilir ve tanısal ikilem yaşanabilir. Bu olgu ile izlem sırasında tanısal bulmacanın çözümlenebildiğine dikkat çekmek istiyoruz.

Anahtar Kelimeler: Yenidoğan,Konjenital afibrinojenemi/hipofibrinojenemi,Kanama diatezi

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1. Introduction

Hereditary fibrinogen diseases are rare and have a spectrum of genetic fibrinogen disorders that develop consequence of the mutations in the components of the fibrinogen secretion caused by errors in transcription, mRNA processing, translation, polypeptide processing, and accumulation. They may be divided into two groups as Type I and Type II. In Type I, the quantitative features of the fibrinogen in the circulation are affected, and there is hypofibrinogenemia (<150 mg/dl) and afibrinogenemia that is characterized with complete deficiency of fibrinogen (<10 mg/dl) [1,2]. As congenital afibrinogenemia/hypofibrinogenemia (CA/CH) has an autosomal recessive transition, its frequency has increased in the communities where marriages among relatives are common [3].

The average plasma fibrinogen concentration is 150-350 mg/dL, and its half-life is approximately four days [1]. The fibrinogen molecule is a homodimer which is produced in the liver, and each of its half parts consists of three pieces of non-identical polypeptide chains (α-, β- and γ chains). Three genes encode these three chains in the fibrinogen molecule (FGA, FGB, and FGG), and all of them are in the long arm of the 4th Chromosome (4q31.3-4q32.1) [1,4].

The clinical phenotype and genotype do not always show parallelism, and the bleeding patterns of two different patients who have the same genotype may show differences [5]. A total of 85% of the cases present with bleeding in the umbilicus in neonatal period. Muscle, joint, CNS, oral cavity bleedings and menorrhagia are reported later in life. Mucosal hemorrhage and hematomas are the most common bleeding findings [6].

The cases who have CH are usually asymptomatic and are diagnosed with routine laboratory tests. Bleeding might develop if there is a different bleeding disorder following or accompanying invasive intervention. The bleeding pattern is similar to that of the CA in symptomatic cases; however, it is milder [7,8,9]. We presented a newborn who has homozygote deletion in the whole FGA gene compatible with CA. The natural course of the congenital fibrinogen disorders and management strategies were reviewed.

2. Case Report

Three-days-old female newborn referred to our clinic for suspect of congenital hemostasis disorder. She was treated for jaundice and had poor feeding in the referring hospital when long-lasting bleeding from veni puncture sites was detected. Complete blood count was normal but the coagulation tests repeated for two times were too long to measure. She was born at 37^{+3} weeks to a G3A1P1 40 years old mother with C-section who had gestational diabetes mellitus and bipolar affective disorder and was under the therapy of multiple antipsychotic medications. 2nddegree consanguinity was present between the 36-year- old father and they had a healthy nine years old daughter.

On admission, the infant appeared well, had normal vital signs and good perfusion. Body weight was 2465 g (25-50 percentile); height was 43 cm (<10percentile); head circumference was 32 cm (25-50percentile); her skin and sclera appeared jaundiced. There were bruises and bleeding in the form of leakage from the venipuncture and injection sites in the arms and legs. Her examination findings were otherwise unremarkable.

The initial laboratory findings were as follows; RBC 5x 10^{12}/L, Hb 19.1 g/L, Htc 56%, MCV 85 fL, WBC 18.3 x 10^{9}/L, Plt 228 x 10^{9}/L. On X100 amplification peripheral smear examination, erythrocytes were normocromicnormocytic and had 76% polymorphonuclearleukocytes, 24% lymphocytes, 15 normal sized clustered platelet are as each, CRP 1 mg/dl (normal range). PT and aPTT were immeasurable; the INR was prolonged to maximum, and fibrinogen was 106 mg/dl, d-dimer was 0.17 (normal). The biochemical analysis, all the values were normal other than the total bilirubin: 9.62 mg/dL; direct bilirubin: 0.19mg/dL; lactate dehydrogenase: 1314 U/L. The abdominal and cranial ultrasonography

were normal. The PT, aPTT, INR, and fibrinogen levels of the parents were found to be normal.

After the septic screening and take blood culture, we introduced empirical antibiotics (ampicillin and amikacin) for early neonatal sepsis; and started fresh frozen plasma infusion, and injected 1 mg intravenous vitamin K. Bleedings stopped after FFP administration, and control PT was 14 seconds; aPTT was 36 seconds; INR was 1.3, and the level of fibrinogen was 69 mg/dl. Blood culture was negative and no relation was found with the mother's drugs and low fibrinogen concentration in the literature. The replitase time and the TT could not be examined in our hospital.

Within three days after the interruption of the FFP support, the following results were obtained; PT: maximum; aPTT: maximum, INR: maximum, fibrinogen: 37 mg/dl. FFP support was continued until normal fibrinogen concentrate was obtained. In a few days bleeding repeated again and controlled with 100 mg/kg fibrinogen concentrate (Haemocomplettan P). One day after the administration of fibrinogen concentrate, PT, aPTT, INR was normal and fibrinogen level was measuredas 69 mg/dL. The genetic examination revealed Whole Gene Homozygote Deletion in the FGA gene (Figure-1). The genetic analysis was compatible with CA. Fibrinogen level of the baby during follow up decreased and our laboratory reported the fibrinojen level <35 mg/dL repeatedly. The diagnosis of CA became clear during follow-up.

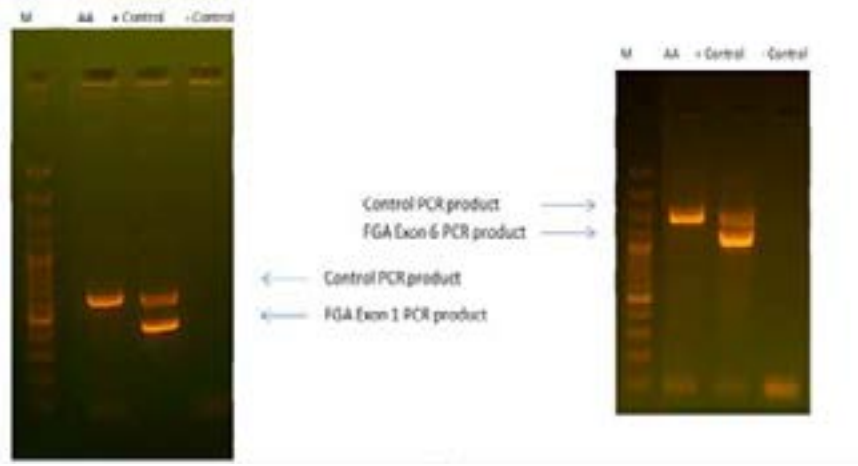

Figure-1: *Whole Gene Homozygous Deletion in FGA gene.*

3. Discussion

A complete history (including family history) and physical examination is necessary for the diagnosis of neonatal bleeding disorders. Bleeding disorder in relatives is a valuable data but a negative family history does not exclude a congenital condition. Bleeding sites does not precisely differentiate primary hemostasis defects from secondary hemostasis defects [orcoagulationtype-bleeding] especially in newborns. In our patient initial studies showed prolongation of PT, PTT, and INR with low fibrinogen level [6]. After exclusion of other conditions that may cause low fibrinogen level, healthy appearance of our patient with bleeding disorder leads us to consider the diagnosis of congenital factor deficiencies.

In our case, on admission, the PT, aPTT and INR were determined to be too long to be measured; and the fibrinogen level was determined to be low (106 mg/dl). According to the fibrinogen level, we thought that the diagnosis was compatible with CH. In the CH, the fibrinogen level is below 150 mg/dl; and

the coagulation tests are prolonged, and TT is the most sensitive test in diagnostic terms [1,4,14]. However, the clinical findings, the early initiation of the disease and the genetic analysis were similar to CA. The laboratory examination of CA is characterized by an unmeasurable low fibrinogen level of less than 10 mg/dl and significantly prolonged PT, aPTT, INR, TT and replitase time. Although we could not show the quantitative level clearly, the fibrinogen level of the infant reported repeatedly low [<35 mg/dL]. The diagnosis of CA became clear during follow-up. The differential diagnosis could be difficult in neonatal period, fibrinogen level decreases in the time. We experienced that diagnosis according to fibrinogen level can be misleading.

These cases usually refer to clinics with bleedings milder than the patients who have hemophilia [10]. In general, CH may appear in the form of prolonged bleeding from medical intervention or operation areas [11]. Akelma et al. [12] shared the results of 105 cases who had congenital factor deficiency, four cases (3.8%) were reported to be diagnosed with CH; one case was reported to have umbilical bleeding, one case had gastrointestinal bleeding and two other patients had prolonged PT and aPTT as the initial findings. All cases had consanguinity between their parents, and half of them had a family history. In this report, CA cases were below the age of one, there were bleedings from the injection sites, and it was also determined that CH cases were diagnosed later. In a multicenter study conducted by Fışkın et al. [13], fibrinogen deficiency (CA/CH) was determined in 15 (9.6%) of the 156 cases who had rare coagulation disorders. The average age of the cases during diagnosis was one month, and the most frequent complaint was intracranial hemorrhage that appeared following traumas or bleedings in the nose [13]. In our patient, the hemorrhage from the medical intervention areas in the form of leakage on the 5thday of life seems atypical for CH amongst the other reported cases. The clinical presentation and genotype were compatible with CA in neonatal period, during follow up fibrinogen level decreased and the diagnostic puzzle completed.

In nearly half of the autosomal recessively inherited CA/CH cases, consanguinity was reported among the parents [14]. Similarly, second degree consanguinity was determined in the parents of our patient. Until now, more than 200 different mutations were defined affecting the quantitative level of the fibrinogen in FGA, FGB and FGG genes [15]. However, new mutations are still reported. In two articles that were published in 2017, a new mutation in the FGB gene was defined in a case from China; and a total of 16 mutations were defined in 15 patients as 10 in the FGA gene; 3 in the FGB gene and 3 in the FGG gene were reported in a study from Pakistan 12 of which were new [16,17]. Defining these mutations, diagnosing and confirming the potential carriers, and characterizing them for a familial diagnosis are important. While the most common mutations resulting with the absence of fibrinogen appear in the gene that encodes the α chain (FGA), patients with CH have mutations in the gene that encodes the γ-chains (FGG) [1, 5, 18]. The genetic analysis of our patient revealed Whole Gene Homozygote Deletion in the FGA gene which was not previously identified in the literature. While the frequently expected mutation in CH is in the FGG gene, the mutation was detected in the FGA gene in our patient which is detected mostly in CA cases.

As a result, although not so frequent as CA or hemophilia, CH cases are among the very rare hemostasis disorders which may appear with abnormal bleedings in various parts of the body especially bleeding in the umbilicus in neonatal period. As for the laboratory works, the fibrinogen levels and TT must be examined to differentiate from hemophilia patients who have long PT and aPTT. In cases who have low fibrinogen levels, the reasons for secondary deficiencies must be excluded before the congenital deficiency is diagnosed; and fibrinogen concentrate must be preferred as the first choice in urgent bleeding control, and if this is not possible, bleeding control must be carried out with FFP or CP. The conventional treatment for fibrinogen deficiencies [in case of bleeding] is episodic treatment, and Fibrinogen Concentrate (FC) must be administered as soon as possible during bleeding. With the 100 mg/kg

fibrinogen concentrate replacement to our patient, the fibrinogen level was 69 mg/dl after 24 hours, and the bleeding was taken under control. Since the administration of FFP or FC will increase the risk of thrombosis when there are no active bleedings, the prophylactic administration is not recommended [18].Our case has become an index case for the family; if the mother becomes pregnant again, the antenatal diagnosis is possible by examining the genetic mutation.

- ✓ *Permission was obtained from the family to make a case report.*

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Osmangazi Tıp Dergisi
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Case Report / Olgu Sunumu

A Rare Cause of Hyperkalaemia: Excessive Potassium İntake with Diet Does Hyperkalaemia Occur After Eating Bananas?

Hiperkaleminin Nadir Nedenlerinden Biri: Diyetle Fazla Miktarda Potasyum Alımı Muz Yeme Sonrası Hiperkalemi Olur mu?

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Abstract

Hyperkalemia is a rare condition after the dietary intake of large amounts of potassium. It may be more likely to occur in patients with impaired renal function and multiple drug use. Since potassium disorders lead to cardiac effects, life-threatening cardiac arrhythmias may occur when they are not recognized or treated. We detected hyperkalemia in the patient who came to our emergency department with a complaint of nausea. The anamnesis of the patient was detailed, and it was learned that the patient had excessive consumption of bananas with diet. It should be borne in mind that there may be problems with excretion of potassium in the elderly and patients with additional diseases. Treatment of our patient in the emergency department was started early and potassium was reduced to normal limits. Dietary intake should be questioned in addition to kidney dysfunction in all patients with hyperkalemia.

Keywords: Hyperkalemia, diet, ECG

Özet

Diyetle fazla miktarda potasyum alımı sonrasında hiperkalemi nadir gelişen bir durumdur. Özellikle böbrek fonksiyon bozukluğu ve çoklu ilaç kullanımı olan hastalarda görülme ihtimali artabilir. Potasyum bozuklukları kardiyak etkilenime yol açtığından tanınmadığı veya tedavi edilmediği durumlarda hayatı tehdit eden kardiyak aritmiler görülebilir. Acil servisimize bulantı şikayeti ile gelen hastada hiperkalemi saptanmıştır. Hastanın anamnezi tekrar alındı ve diyetle aşırı miktarda muz tüketimi olduğu öğrenildi. Yaşlılarda ve ek hastalığı olan hastalarda potasyumun atılımı ile ilgili problemler olabileceği akılda tutulmalıdır. Hastamızın acil serviste tedavisi erken dönemde başlanarak ve potasyumu normal sınırlara düşürülmüştür. Hiperkalemi saptanan tüm hastalarda böbrek fonksiyon bozukluklarına ek olarak diyet alımı da sorgulanmalıdır.

Anahtar Kelimeler: Hiperkalemi, diet, EKG

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1. Introduction

Hyperkalemia is one of the important life-threatening clinical scenarios in the emergency department. Mainly due to cardiac arrhythmia and cardiac arrest caused, it should be diagnosed at an early period and its treatment should be started (1). Causes of hyperkalemia include; excessive potassium intake with diet, decreased potassium excretion, shift through the cell membrane to the extracellular compartment. Hyperkalemia, as a result of excessive potassium intake, is very rare in those with normal kidney function. Hyperkalemia can be compensated by the renal mechanisms that absorb potassium into the cell and ensure its excretion from the kidney.

In the literature, cases have been reported about hyperkalemia due to the consumption of orange juice, tomato juice, apple juice, apricot, dried fruit, and banana (2). Cardiac arrhythmias and ST-segment elevation after apricot and banana consumption have been shown, especially in patients with renal dysfunction (3).

Normally, the potassium level should be 3.5-5.0 mEq / L in serum. However, clinically significant effects are seen when the serum potassium level rises above 6.5 mEq / L. Patients may present with asymptomatic muscle cramps, paralysis, decreased deep tendon reflexes, and arrhythmias (1).

In this case report, we present a patient who admitted to the emergency department with the complaint of nausea and vomiting and who developed hyperkalemia because he ate too much banana and dried fruit in his diet.

2. Case Report

A 60-year-old male patient admitted to the emergency department with a complaint of nausea. The patient who had Type 2 diabetes mellitus and coronary artery disease in his past medical history, also complanied of watery diarrhea for a week. The vitals of the patient were: Blood Pressure: 120/70 mmHg, a heart rate of 80 beats/min, body temperature of 36.5 °C, and oxygen saturation of 99%. His medications include nebivolol, metformin combined with vildagliptin, trimetazidine, acetylsalicylic acid, amlodipine, atorvastatin, and ticagrelor. Peaked T-wave were noticeable in the all leads of ECG. Therefore, ST-segment elevation was associated with suspected AMI or hyperkalemia, and treatment for the acute coronary syndrome was initiated. Laboratory parameters were: Cr: 1.39 mg/dl, BUN: 24.7 mg/dl, GFR: 55.08 ml/min, K: 7.75 mEq/L, pH: 7.352, and HCO3: 20 mmol/L. During the observation in ED, the widening of QRS complexes developed in the subsequent ECG (Fig.1B), prompt intravenous glucose and insulin and calcium infusions, inhaled salbutamol, to enhance potassium uptake into the cells. When the patient was questioned again, he told that he took his medications regularly and did not take any other medication. However, since he had diarrhea for several days, he stated that he ate 5 large bananas, a large number of raisins and walnuts the day before. In the ECG of the patient whose potassium level decreased, T sharpness decreased as shown (Fig.1C). High sensitivity troponin levels were all in normal limits. The patient's ECG further recovered after 1 day of follow-up, and the potassium level decreased to 5.3 mEq/L (Fig.1D and Fig.1E). In the re-evaluation after discharge, the patient evaluated in polyclinic, it was observed that potassium levels were within normal limits.

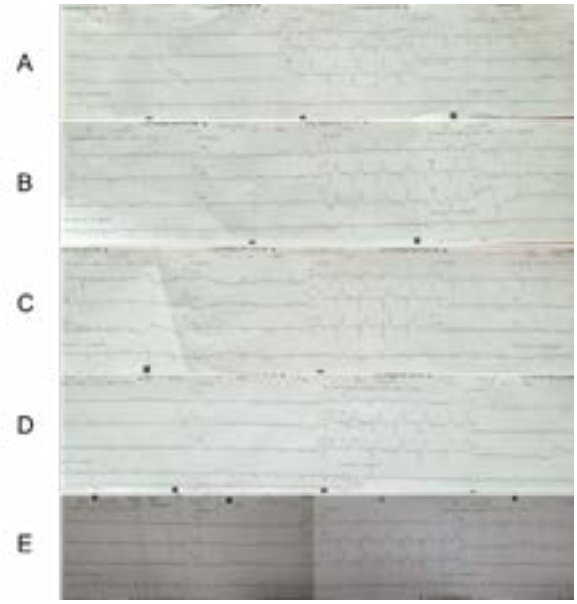

Figure 1. The ECG findings of the patient.

A) First ECG 19:40 peaked T waves. B) 20:20 peaked T waves and wide QRS. C) 21:50 After treatment narrow QRS. D) Next day 13:00 E) 16:00 normal ECG

3. Discussion

Hyperkalemia rarely develops as a result of excessive intake of potassium with diet. Hyperkalemia is an important clinical condition that should be considered, especially in patients with beta-blocker use and in diabetic patients. It should be acknowledged that it can be life-threatening leading to ventricular arrhythmias. In a case report published in 2012, ventricular tachycardia due to hyperkalemia was described (3).

Diet-related hyperkalemia is a very rare cause of hyperkalemia (4,5). A decrease the kidney's potassium excretion capacity both increases the susceptibility of the organism to diet-related hyperkalemia and causes transcellular potassium transitions in the distal nephron (5). Therefore, diet-related hyperkalemia is expected to occur more in patients with impaired renal function (4) and diabetes (6). The cause of hyperkalemia may be excessive banana consumption or drug side effects. In particular, potassium-sparing diuretics and beta-blockers can lead to hyperkalemia. In our case, the patient was not on potassium-sparing diuretics and it was acknowledged that he did not make any changes in the beta-blocker dose he had used for months. Also, beta-blocker toxicity was not considered in the patient because bradycardia was not present. The amount of potassium with dietary intake may not be tolerated, even mildly impaired renal function, and due to the use of beta-blockers.

An average banana contains 360 mg of potassium per 100 grams (7). It has been shown that the amount of potassium intake in exercise increases serum potassium, although kidney function is normal (8). Therefore, it should be kept in mind that hyperkalaemia will develop even if there is no underlying disease.

When ECG findings are evaluated, serum potassium levels, especially above 8 mEq / L, may lead to QRS axis changes, intraventricular blocks, sinus wave pattern, and VF and asystole-related deaths. When moderately (Serum potassium 6.5-8.0 mEq / L) elevated, QRS width, decreased P wave amplitude and prolonged PR segment can be observed (9). In our case, QRS widening was

observed in the 2nd ECG. Since severe hyperkalemia may be observed in the absence of treatment, the ECG findings of hyperkalemia should be well known by physicians.

Studies have shown that patients do not systematically evaluate dietary properties (10). In this respect, patients with medications that affect potassium metabolism, kidney failure, and diabetes should be informed about their potassium content in their diets when prescribing these drugs.

Diet-related hyperkalemia should be kept in mind in patients with diabetes, renal failure, the elderly, and those who are on polipharmacy. In patients with symptoms and laboratory findings, it will be appropriate to warn patients, although the treatment does not change.

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Derleme / Review

COVID-19 Pandemisinde Kullanılan İlaçlar, Etki Mekanizmaları ve Etkililikleri

Drugs Used in the Treatment of COVID-19 Pandemic, Their Mechanisms of Action and Efficacy

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Özet

Aralık 2019' da Çin' in Wuhan kentinde ortaya çıkan koronavirüs ailesinden olan COVID-19 tüm dünyada pandemiye yol açmıştır. Bu virüsün daha önce SARS-CoV ve MERS-CoV olarak salgın yapmış koronavirüsler ile genetik yakınlığı vardır. COVID-19 hastaları, ciddi akut respiratuvar sendrom (ARDS), ağır pnömoni tablosu, hematolojik bulgular, dissemine intravasküler koagülopati (DIC) ve sepsis gibi ağır tabloların yanısıra koku kaybı, bulantı, kusma, ishal gibi gastrointestinal sistem bulguları ya da sadece cilt döküntüleri ile de hastanelere başvurabilmektedirler. Akut dönemde makrofaj aktivasyon sendromu (MAS) ve sitokin fırtınası sebebiyle ağır inflamasyon tablosuna sebep olmaktadır. Tedavide, SARS-CoV ve MERS-CoV ile oluşan hastalık durumlarında kullanılan ilaçlar denenmektedir. Proflaksi ve tedavide klorokin, hidroksiklorokin kullanılırken ağır pnömoni durumlarında, ilave olarak azitromisin tedaviye eklenir. Hastalığın seyrine göre favipiravir, lopinavir, ritonavir, remdesivir, ribavirin gibi tedavide kullanılan/ denenen ilaçlara yardımcı ilaçlar olarak antisitokin-immunomodulatörler (tosilizumab, anakinra, sarilumab, bevasizumab, ekulizumab), kortikosteroidler, immünoglobilinler, interferonlar ve antiagregan-antiinflamatuvar (dipiridamol) ilaçlar kullanılır. Bu hastalığın seyri sırasında oluşabilecek koagülasyonu önlemek amacıyla profilaktik olarak düşük molekül ağırlıklı heparin (enoksaparin) kullanılabilir. COVID-19 semptomları mevsimsel ve semptomatik nedenlerle influenza ile karışabilir. İnfluenza olması durumunda tedavide oseltamivir kullanılır. Normal şartlarda herhangi bir tedavisi olmayan COVID-19 için aşı ve ilaç çalışmaları hız kazanmıştır. Ancak bu sürecin en az bir yıl kadar sürebileceğini söylemekte yarar vardır. Hatta bu hastalıkla mücadelede kök hücre çalışmaları da yapılmaktadır.

Anahtar kelimeler: Pandemi, koronavirüs, COVID-19, farmakolojik yaklaşımlar

Abstract

COVID-19, which belongs to a coronavirus family that emerged in Wuhan-China in December 2019, has caused pandemics worldwide. This virus has genetic affinity with previous coronaviruses, which have been outbreaks as SARS-CoV and MERS-CoV. COVID-19 patients have severe acute respiratory syndrome(ARDS), severe pneumonia, hematological findings, disseminated intravascular coagulopathy(DIC) and sepsis and also have signs of gastrointestinal system such as loss of smell, nausea-vomiting, diarrhea and sometimes only skin manifestations. In acute period, it causes severe inflammation due to macrophage activation syndrome(MAS) and cytokine storm. In treatment; drugs used in the treatments of SARS-CoV and MERS-CoV, are being tried. While chloroquine/ hydroxychloroquine are used in prophylaxis and treatment, in cases of severe pneumonia, azithromycin is additionally added to the treatment. According to the course of the disease, drugs which are used/being tried at the treatment such as favipiravir, lopinavir, ritonavir, remdesivir and ribavirin could be combined with adjuvant drugs such as anticytokine-immunomodulators (tocilizumab, anakinra, sarilumab, bevacizumab, eculizumab), corticosteroids, immunoglobulines, interferons and antiaggregant drugs (anti-inflammatory drugs) are used as auxiliary drugs. Heparin (enoxaparin) can be used prophylactically, to prevent coagulation in course of this disease. COVID-19 symptoms can be confused with influenza for seasonal and symptomatic reasons. In case of influenza, oseltamivir is used for treatment. Vaccine and drug studies have accelerated for COVID-19, which does not have any treatment under normal conditions. But it would be beneficial to mention that this process may take at least one year. In fact, stem cell studies are also carried out to combat this disease.

Keywords: Pandemic, coronavirus, COVID-19, pharmacological approaches

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1. Giriş

COVID-19 pandemisi aralık 2019' da Çin'in Wuhan kentinde başlayıp, koronavirüs (ciddi akut respiratuvar sendrom koronavirüsü) kaynaklı olarak ortaya çıkmıştır (1). Bu yeni beta koronavirüs (nCOV); SARS-CoV ve MERS-CoV ile genetik yakınlıklarına bağlı olarak oldukça benzerdir. Bu nedenle epidemiyolojik takip, tanısal testler, önleyici ve tedavi edici stratejilerin belirlenmesinde SARS-CoV' un viral genom dizilimi oldukça önemlidir (2).

Şu ana kadar COVID-19 vakalarında herhangi bir potansiyel tedavinin olduğuna dair bir kanıt olmamasına rağmen, bu yazıda olası tedavilerle ilgili bir derleme oluşturduk.

SARS ve MERS virüs tedavisinde etkili olan bazı ilaçların COVID-19 tedavisi için potansiyel aday olduğu düşünülmektedir. Aslında SARS ve MERS tedavisiyle ilgili çalışmaların meta analizleri de herhangi bir tedavi rejimine dair fark ortaya koyamamıştır (3, 4). COVID-19 tedavisi için bazı ümit vaad eden ilaçlarla olası tedaviler oluşturulmuştur. Bu olası tedaviler aşağıdaki şekillerde olabilmektedir.

Klorokin ve Hidroksiklorokin

Klorokin ve hidroksiklorokin, malaryanın önlenmesinde ve tedavisinde ve ayrıca sistemik lupus eritematozus ve romatoid artrit gibi inflamatuvar hastalıkların tedavisinde uzun süredir kullanılan ilaçlardır(5). Etkilerini konak hücrede glikolizasyonun, proteolitik sürecin ve endozomal asidifikasyonun inhibisyonu yoluyla virüsün hücreye girişini engelleyerek göstermektedirler. Ayrıca bu ajanlar konak hücrede sitokin üretiminde, otofaji ve lizozomal aktivitede azalma yoluyla immünmodülatör etki göstermektedirler (6, 7).

SARS ve MERS tedavisinde klorokin ve hidroksiklorokinin etkili olduğuna dair herhangi bir kanıt mevcut değildir. Ancak yapılan COVID-19 vakalarında radyolojik bulgularda iyileşme, viral arınmada artış ve hastalığın ilerlemesini sınırladığı bildirilmektedir (8). Fransa'da 36 hastayla yapılan bir çalışmada 8 saatte bir oral yoldan alınan 200 mg dozunda hidroksiklorokinin standart destekleyici tedavi alan kontrol grubuna kıyasla virüs yükünü azalttığı bildirilmiştir. Çalışmayı yapanlar ayrıca 6 hastada hidroksiklorokin tedavisine azitromisin eklenmesinin hidroksiklorokin monoterapisine üstünlük gösterdiğini de bildirmiştir (9).

Hasta sayısının düşük olması ve hidroksiklorokin içeren ilaçların iyi tolere edilememesi ya da hastalık seyrinin kötüleşebilmesi gibi sebeplerden dolayı tedavisinin erken sonlandırılması, ya da kombinasyonlarla kullanımında viral yük farkı ile farmakovijilans açısından klinik ve güvenlilik sonuçlarının belirtilememesi bu sınırlamalar arasında sayılabilir. Bu sınırlamalara kardiyotoksisite ile ilgili endişeler özellikle aritmiler de eklenmiştir.

Çin' de yapılan çalışmada günde 400 mg, 5 gün hidroksiklorokin tedavisi ve standart tedavi (destek tedavisi, interferon ve diğer antiviraller) alan veya sadece standart tedavi alan randomize 30 hastada virolojik bulgularda bir fark bulunamamıştır. 7. Günde bu iki grup arasındaki viral arınma %86,7' ye %93,3 gibi bir oranla benzer bulunmuştur(10). Özellikle Sağlık çalışanlarında klorokin profilaksisi ve yüksek riskli temas sonrası profilaksisi ile ilgili çalışmalar da vardır. COVID-19 için klorokin tedavi dozu, günlük oral 1 veya 2 defa 500 mg olduğu belirtilmekle beraber (11) klorokinin güvenlilik ve etkinliğinin hesaba katılması için hala veri yetersizliği mevcuttur.

SLE tedavisinde hidroksiklorokinin önerilen dozu günlük oral yoldan 400 mg' dır (12). Buna rağmen bir çalışmanın sonucuna göre ağır pnömonili COVID-19 için önerilen hidroksiklorokin optimal dozu ilk gün günde 2X400 mg yükleme dozu, sonrasında günde 2X200 mg şeklinde olmalıdır (13). Ancak her koşulda COVID-19 için en uygun dozun belirlenmesi için ileri çalışmalara ihtiyaç vardır.

SLE ve malarya hastalarından edinilen geniş çaplı tecrübelerden yola çıkılarak klorokin ve hidroksiklorokinin iyi tolere edilen ilaçlar olduğu söylenebilir. Yine de iki ajan nadiren

olsa da hipotansiyon, kardiyomyopati, QT uzaması, hipoglisemi, nöropsikiyatrik etkiler ve retinopati gibi ciddi yan etkilere sebep olabilir (<%10). Ayrıca abdominal kramp, hepatotoksisite ve bu bağlamda karaciğer fonksiyon testlerinde artış, anoreksi, ishal, bulantı-kusma, ürtiker, anjiyoödem dahil anafilaktik reaksiyon gibi non-spesifik advers etkiler de görülmektedir. Makülopati ve maküler dejenerasyonlar geri döndürülemez olabilir. Uzun süreli veya yüksek dozda 4-aminokinolin tedavisi alan hastalarda retinal pigmentasyon değişiklikleri (boğa gözü görünümü) ve görme alanı defektleri (parasantral skotomlar) ile geri dönüşümsüz retinopati bildirilmiştir. Nöronal sağırlık; kulak çınlaması, önceden var olan işitme hasarı olan hastalarda işitme azalması ve kaybı dışında; proksimal kas gruplarının progresif zayıflığı ve atrofisine yol açan iskelet kası miyopatisi veya nöromiyopati, tendon reflekslerinin depresyonu ve anormal sinir iletimi de görülebilir. Ayrıca Pansitopeni, aplastik anemi, geri dönüşümlü agranülositoz, trombositopeni ve nötropeni ile G6PD (Glükoz 6 fosfat dehidrogenaz) eksikliği olan hastalarda hemolitik anemi de yapabilirler. Yan etkileri içinde nöropsikiyatrik değişimler; özellikle psikoz, deliryum, anksiyete, ajitasyon, uykusuzluk, konfüzyon, halüsinasyonlar, kişilik değişiklikleri, depresyon ve intihar davranışı gibi nöropsikiyatrik değişiklikler nadiren olsa da görülebilmektedir (14).

Bu nedenle bu ilaçların kullanımı sonucu mu, yoksa hastalığın kendisi mi bu bulguları yapmaktadır, karışabilir. Klorokin yüksek dozlarda uygulanırsa veya kombinasyonlarla kullanımlarında bu türlü advers etkilerin oluşması riskinin daha fazla görülebileceği de oldukça açıktır.

COVID-19 tedavisi için ise belirlenen dozlar ve kullanım süresinin kısalığı nedeniyle klorokin için anlamlı bir yan etki bildirimi henüz olmamıştır. Gebelikte klorokin ve hidroksiklorokin kullanımı genel olarak güvenli kabul edilmektedir. 588 hastayı içeren 12 çalışma üzerine yapılan bir derlemede gebelikte kullanılan klorokin veya hidroksiklorokinin şimdiye kadar infantlarda oküler toksisiteye sebep olduğuna dair bir bulguya rastlanmamıştır (12). Olası İlaç-ilaç etkileşmelerini klorokin fosfat CYP2D6 ve CYP3A4 enzimleri aracılı yaparken; hidroksiklorokin fosfat CYP2D6 ve CYP3A4, CYP3A5 ile CYP2C8 enzimleri üzerinden etkilerini yapmaktadırlar Bu enzimlerle metabolize olan ilaçlarla özellikle etkileşme beklenmektedir(2).

Oxford Üniversitesinden Professor Peter Horby ve Prof Martin Landray ın yürütücülüğünde yapılan bir klinik çalışmada tedavide hidroksiklorokinin etkisi araştırılmıştır. Bu çalışmada 1542 hasta bu ilaç ile tedavi olurken 3132 hastaya standart tedavi uygulanmıştır. 28 Günlük tedavi sonunda hidroksiklorokin kullananlarda % 25,7 ölüm, kullanmayanlarda ise % 23.5 ölüm görülmüştür. Sonuç olarak da hidroksiklorokin kullanımı ile ölümlerin arttığı bildirilmiştir (15).

Başka bir çalışmada ise COVID-19 la yüksek riskli veya orta derecede riskli maruziyetten sonra, hidroksiklorokin kullanıldığında veya 4 gün içinde maruz kalma sonrası profilaksi olarak kullanıldığında COVID-19 ile uyumlu hastalığı veya buna bağlı gelişen enfeksiyonu önlemediği de bildirilmiştir (16).

Favipiravir

T-705 olarak da bilinen bu ilacın ribofuranasil-5-trifosfat olan pürin nükleotidin ön ilacıdır. Virüs replikasyonunu durduran RNA polimeraz inhibitörüdür. Favipiravir ile ilgili preklinik çalışmaların çoğu aynı aileden olan Ebola ve influenza virüsleri içindir. Ancak diğer RNA virüslerine karşı da geniş aktiviteye sahiptir. COVID-19 tedavisi için bu ilacın yüksek dozları tercih edilmelidir (17). Tavsiye edilen yükleme dozu 12 saatte bir 2400-3000 mg'dır. İdame olarak ise 12 saatte bir 1200-1800 mg'dır. Yarılanma ömrü ise 5 saattir (18). Orta dozlarda iyi tolere edilirken yüksek dozlarda advers etkisi fazladır (17, 19). Özellikle hiperürisemi, ishal, nötrofillerde azalma ile transaminazlarda artmaya neden olurlar. İlaç-ilaç etkileşmelerini ise CYP2C8, aldehid oksidaz inhibisyonu ve ksantin oksidazlar aracılı oluşmaktadır (2). Şimdilerde Japonya' da influenza tedavisi için de kullanılmaktadır.

COVID-19 tedavisinde kullanımları için hala sınırlamalar vardır. COVID-19 tedavisi için yapılan klinik çalışmalarda, favipiravir kullanan orta şiddetli olgularda daha iyi sonuç verirken, şiddetli olgularda istatistiksel olarak anlamlılık yoktur (20). Favipiravir ülkemizde COVID-19 tanısı alan bireylerde Klorokin ve hidroksiklorokin gibi rutin tedavide kullanılan bir ilaçdır. Ayrıca, önceki çalışmada favipiravir'in teratojenik bir ilaç olarak sınıflandırıldığını, yani gebeliğin erken devresinde embriyonun gelişmesini geciktirme ve ölümüne sebep olabilmektedir. Bunun dışında da 4 değişik tip hayvan türünde, maymunlar dahil, teratojenik etki gösterdiği belirlenmiştir. Hayvan deneylerinde yapılan histopatolojik tetkikler testislerde patolojik değişiklikler ve sperm hasarları tesbit edilmiştir. Çocuk doğurma çağında olan kadınlar ve bunların eşlerinin doğum kontrolü yöntemlerini kullanmaları gerekir. İlaç erkeklerde seminal sıvı ile uterusa erişebilir, spermde hasara sebep olabilir ve bu ilacı kullanan erkeklerin fertilize ettiği embriyolarda da terotojenik etki görülebilir. İlaç verilmeden önce kadınlarda mutlak gebelik testi yapılmalıdır, buna rağmen gebeliğin erken dönemimde testlerin negatif sonuç verebileceği de unutulmamalıdır (21).

Başka bir çalışmada da Umifenovir ile karşılaştırıldığında çok etkili bulunmamakla birlikte özellikle ateş ve öksürük şikâyetlerini azalttığı bildirilmiştir (22)

Diğer ciddi yan etkileri arasında şok, anaflaksi, pnömoni, fulminan hepatit, sarılık, toksik epidermal nekroliz, Stevens-Johnson sendromu, akut böbrek hasarı, löksit-nötrofil ve trombosit sayılarında azalma, şuur bozukluğu, anormal davranışlar, deliryum, hallusinasyonlar, delüzyon, konvülziyonlar, hemorajik kolit sayılabilir (23).

Lopinavir/ ritonavir ve Diğer Antiretroviraller

Lopinavir/ritonavir FDA tarafından HIV tedavisi için onay almış olup, 3-kemotripsin benzeri proteaz (3CL proteaz) inhibisyonu aracılığıyla koronavirüslere karşı in vitro aktivite göstermektedir (24, 25). Bu kombinasyonla ilgili SARS ve MERS tedavisi üzerine yapılan sınırlı sayıda çalışma mevcuttur ve bunların çoğu SARS üzerinedir. İlaç uygulamasının erken viral replikasyon pikinde yapılması oldukça önemlidir. Çünkü bu ajanlarla geç başlanan tedavinin klinik sonuçlar üzerinde hiçbir etkisinin olmadığı görülmüştür. Lopinavir/ritonavir' in COVID-19 tedavisinde etkisi ile ilgili ilk yayınlanan sonuçlar genellikle küçük çaplı retrospektif randomize olmayan kohort çalışmalar ve olgu sunumlarının sonuçlarıdır. Bu da lopinavir/ritonavirin tedavisinin COVID-19 üzerine etkilerini belirlemeyi güç hale getirmiştir (26, 27).

Lopinavir/ritonavir kullanımı en fazla 14 gün boyunca günde iki defa 400mg/100mg'dır. Bu tedavi uygulanırken beraberinde kullanılan diğer ilaçların dikkatle seçilmesi ve monitorizasyonun sağlanması oldukça önemlidir. En sık görülen gastrointestinal yan etkiler arasında bulantı, kusma, ishal, pankreatit, hepatotoksisite ve kalpte iletim anormallikleri sayılabilir (28). COVID-19 hastalarında kombinasyon tedavisi bu yan etkileri daha da arttırabilir. Çünkü COVID-19 hastalarının yaklaşık %20-30' u artmış transaminazlarla karşımıza çıkmaktadır (26). Son zamanlarda yapılan bir çalışmada bu tedavi rejimini alan hastaların yaklaşık %50' sinde gastrointestinal yan etkiler görüldüğü ve %14' ünün bu yan etkiler sebebiyle tedaviye devam edemediği bildirilmiştir (28). Artmış alanin transaminaz seviyesi pek çok COVID-19 araştırmasında red kriteri olarak kabul edilmiştir. Bu nedenle lopinavir/ ritonavir'e bağlı gelişen hepatotoksisite, hastaların diğer ilaçlardan faydalanmasını kısıtlamaktadır. Major ilaç-ilaç etkileşimlerinde de CYP 3A4 enzim inhibisyonu önemlidir. Ayrıca P-glikoproteinlerinde rolü vardır (2). Bu ilaçlarla ilgili 127 hastada yapılan bir çalışmada tek başlarına değil, İnterferon 1 beta ve ribavirin ile kombine kullanıldıklarında tedavide daha etkili bulunmuşlardır (29). Başka bir çalışmada da lopinavir-ritonavir in özellikle şiddetli COVID-19 lu hastalarda tedavi edici bir yararının olmadığı yönündedir (28).

Remdesivir

Nükleotid analoğu olarak tanımlanan Remdesivir, antiviral ilaçlar grubundadır. Bir adenozin nükleotid analoğu olup etken maddesi GS-441524 adlı aktif bir maddedir. Hücre içinde nükleotid (adenosine nükleotid trifosfat) anoloğu olarak viral RNA bağımlı RNA polimeraz etkisini azaltarak viral RNA oluşumunu azaltmaktadır. Bu ilaç koronavirüs, flavivirüs gibi RNA virüslere karşı antimikrobiyal tedavi taramaları sırasında keşfedilmiştir. Remdesivir, özellikle Ebola virüsün yoğun yaşandığı süreçte yapılan araştırma ve geliştirme çalışmaları sırasında konak polimeraz selektivitesi göstermiştir (30). Remdesivir geniş spektrumlu olup, birçok CoV virüsler enfeksiyonlara karşı güçlü aktivite gösterir (31). Deneysel olarak yapılan MERS-CoV ile enfekte fare akciğerlerinde remdesivir, diğer tedavilerle karşılaştırıldığında, akciğer hemorajileri ve viral akciğer bulgularını azaltmıştır (32).

Klinik çalışmalarla Faz-1 aşamasında tek ve çoklu dozlarının kullanımı ile farmakokinetik ve güvenlik çalışmaları da yapılmıştır. 3-225 mg iv dozlarının karaciğer ve böbrek fonksiyonları açısından iyi tolere edildiği, yarılanma ömrünün 35 saatten fazla olduğu bildirilmiştir. Çoklu dozları izlendiğinde ise reversibl olarak aspartat aminotrasferaz, alanin transaminaz aktivitesi artmıştır. Bu süreçte ne hepatik ne de renal patoloji gösterilmemiş fakat tedavinin başlangıcında hastalarda glomerüler filtrasyon hızı 30mL/min olmuştur. İlk klinik kullanımları ebola virüs tedavisidir (33). Bununla birlikte COVID-19 için tedavide başarılı olabileceği bildirilmiştir (34). Orta ya da şiddetli COVID-19 hastaları için antiviral etkinliği konusunda klinik çalışmalar devam etmektedir. Bu ilacın COVID-19 tedavisinde kullanımı için FDA Mayıs 2020 de ‘’acil kullanım izni’’ ni 2 çalışmaya dayanarak vermiştir. Birinci araştırma Wang ve ark. tarafından 237 hastada yapılan ve remdesiviri etkisiz bulan çalışmadır (35). Diğeri ise ABD Ulusal Sağlık Enstitüsü (NIH) tarafından desteklenen ACTT-1 çalışmasıdır. Bu klinik araştırmada 10 günlük remdesivir kürü alan hastaların standart tedaviye göre hastanede yatma sürelerinin 4 gün kısaldığı (15 gün yerine 11 gün), fakat ölüm oranında bir değişiklik yapmadığı ortaya çıkmıştır (36). Özellikle advers etkileri açısından gebeler ve 18 yaş altı çocuklarda incelenmeye ihtiyacı vardır. Reversibl olarak transaminazları artırırlar. Ayrıca nefrotoksiktirler, özellikle kreatin klerensinde azalmaya neden olurlar. İlaç-ilaç etkileşmelerinde ise CYP3A4 enzim inhibisyonu ya da indüksiyonu yaptığına dair önemli bir bilgi de yoktur (2) Remdesivirin etkinliğine dair hala sorunlar ve şüpheler devam etmektedir. Bu nedenlerle ilacın kullanılabileceği optimal hasta topluluğu ve tedavi süresi de henüz bilinmemektedir. ABD ve Avrupa’da ruhsat almış olup, bu ilacın COVID-19 da kullanımı ile ilgili olarak birçok bilinmezinin olduğu da bir gerçektir.

Ribavirin

Ribavirin, viral RNA bağımlı RNA polimerazı inhibe eden bir guanin analoğudur. Diğer Corona ailesi üzerine olan etkisi onu COVID-19 tedavisi için de bir aday haline getirmiştir. Bununla birlikte ribavirinin SARS-CoV üzerine in vitro etkinliği kısıtlıdır ve viral replikasyonun inhibisyonu için yüksek konsantrayonu ve ya kombine tedavi olarak uygulanması gerekmektedir. Yapılan çalışmalarda hastalara intravenöz ve enteral uygulama yapılmıştır. Ama inhale tedaviye dair bir kanıt bulunmamaktadır (3, 37).

Ribavirin kullanımı sırasında oluşabilecek advers etkiler açısından en çok doz bağımlı şiddetli hematolojik toksisite görülmektedir. Bu bağlamda yapılan SARS çalışmalarında uygulanan yüksek doz ribavirin tedavisi sırasında hastaların %60’ ından fazlasında hemolitik anemiye sebep olduğu gözlenmiştir (3). Benzer endişeler MERS üzerine yapılan en büyük gözleme dayalı çalışmada da ribavirin ve interferon tedavisi alan hastaların yaklaşık %40’ında kan transfüzyonu gereksiniminin ortaya çıkmasıyla yaşanmıştır (38). SARS tedavisi için ribavirin kullanan hastaların %75’inde ise transaminazlar yükselmiştir (3). Ribavirin teratojen olduğu için gebelikte de kontrendikedir (39).

Ribavirinin SARS, MERS gibi coronalar üzerine etkisine dair yetersiz veriler ve

hepatotoksisitesi, nefrotoksisitesi ve gebelerde ki teratojenitesi göz önüne alındığında, COVID-19 tedavisinde sınırlı bir yeri olduğu söylenebilir. Eğer kullanılacaksa da, lopinavir-ritonavir ile kombinasyon şeklinde kullanımı en fazla klinik yararı sağlayacak kullanım şekli olacaktır (29). Bu pandemi sürecinde standart bir tedavi protokolü olarak da ne tek başına, ne de kombine olarak ülkemizde ve üniversitemizde kullanılamamıştır.

Oseltamivir

Oseltamivir, İnfluenza tedavisi için onay almış bir nörominidaz inhibitörü ilaç olup, SARS-CoV-2' ye karşı etkili olduğu konusunda herhangi bir bilgi yoktur. COVID-19 ortaya çıktığında, influenzanın pik yaptığı mevsim olması nedeniyle tanı konuncaya kadar olan süreçte hastaların tedavisinde kullanılmıştır (40). Bu ilaçla bağlantılı birçok klinik çalışmaların sonucunda da COVID-19 ile ilgili bir tedavi sağlamadığı görülmüştür. Bu nedenle; COVID-19 ile bulgular açısından özellikle bahar aylarında karışan influenza hastalığı tedavisinde spesifik olarak etki göstermektedir.

Arbidol olarak da bilinen diğer bir influenza tedavisinde kullanılan ilaç olan umifenovir ise zarflı, virüslerin membran geçişlerini inhibe eden ve S-protein/ACE2 enzimini hedef alarak etki göstermeyi amaçlayan bir ajandır (41). Bu ilaç Rusya ve Çin' de influenza proflaksisi ve tedavisi ile SARS için kullanılabileceği yönündeki çalışmalardan yola çıkarak COVID-19' un tedavisinde kullanılmak üzere onay almıştır (42). Bu ilaç; influenza tedavisi için günde her 8 saatte 200 mg oral olacak şekilde kullanılmakta olup, COVID-19 tedavisinde kullanılacak dozu henüz belli değildir. Randomize yapılan bir çalışmada tedavide 9 gün kullanan hastalar bu tedaviyi hiç almayan hastalarla kıyaslandığında düşük mortalite hızı oluşturmuştur (%0-16) (43). Aslında bu sınırlı hastada yapılan gözlemsel çalışma, umifenovirin COVID-19 tedavisi için etkili olduğunu da göstermez. İleri çalışmalara ihtiyacı olan bir çalışmadır. Bu ilaç kullanımı sırasında ciddi alerjik reaksiyonlar, hepatotoksisite, transaminazlarda belirgin artma ile gastrointestinal sistem bulguları görülmektedir. İlaç-ilaç etkileşmelerini de CYP3A4 enzim inhibisyonu/ indüksiyonu şeklinde oluşturmaktadır (2).

İnterferonlar

İnterferon alfa ve beta nın; koronavirüs tedavisinde, özellikle interferon beta nın ise MERS tedavisinde etkili olabileceğine dair çalışmalar mevcuttur (3, 4). Bunlar da diğer ilaçlar gibi gecikmiş tedavide etkinliğini sınırlayabilir. Ancak klinik çalışmalarla, in vitro ve diğer deneysel çalışmalar arasında fikir ayrılıkları olabilir. Yapılan çalışmalar, interferonların SARS-CoV-2 tedavilerinde kullanılmasını önermemektedir. Baricitinib, imatinib, dasatinib ve siklosporin gibi çeşitli immunomodülatör ilaçların, SARS-CoV-2 inhibisyonundaki olası mekanizmalar üzerinde etkileri vardır (44-48). Bununla beraber bu ilaçları tedavide kullanmak için ne hayvan ne de insan çalışmaları yeterli değildir. Bu ajanların koruyucu oldukları düşünülebilir.

Akut respiratuvar distres sendromlarında (ARDS) ve akut akciğer enfeksiyonları ile oluşan inflamasyonu önlemede kullanılırlar. Bununla beraber sekonder enfeksiyon oluşumuna da zemin hazırlarlar. Bu grup ilaçların COVID-19 tedavisinde kullanımları ile ilgili olarak sınırlamalar olmakla beraber diğer viral pnömonilerin tedavisi için kullanılabilirler (49). Yapılan çalışmalarda kan ve solunum yollarından virüsün temizlenmesini geciktirdiği, sağ kalımda artmaya neden olmadıkları, hiperglisemi, psikoz ve vasküler nekroz geliştirdikleri gösterilmiştir. Yapılan klinik bir çalışmada ise influenze pnömonisi tedavisi için kullanılmış olup mortalite ve sekonder enfeksiyon riskini artırmışlardır (50). Viral enfeksiyonlardan ziyade bakteriyal enfeksiyonlarda etkili oldukları düşünülmektedir (49). COVID-19' lu hastalarda ARDS gelişen olgularda metil prednizolon kullanımı ile ölüm riskinin azaldığı bildirilmiştir (51). Kronik obstriktif akciğer hastalığı (KOAH) alevlenmelerinde veya inatçı şok durumlarında ki COVID-19' lu hastalar için önerilebilirken yine de rutin tedavide yararından ziyade potansiyel bir zararı söz konusu olabilir. Sonuç olarak

Mekanik olarak havalandırılan ARDS hastaları için, sistemik kortikosteroidlerin kullanımına lehinde veya aleyhinde öneride bulunmak için yeterli kanıt yoktur (52).

İmmunomodülatörler ve Antisitokinler

Monoklonal antikorlar, COVID-19' lu hastalarda yardımcı potansiyel ilaçlardır. Sitokin fırtınası, immün yanıtlara bağlı oluşan akciğer ve diğer organ hasarlarında fizyopatolojik bozulmaların altında yatan nedenleri düzeltmede kullanılırlar (53). Özellikle IL- 6' nın inflammasyondan sorumlu olduğu ve IL-6 sitokinlere karşı bu monoklonal antikorların kullanıldığı çalışmalar vardır (54). Bunlara örnekler verecek olursak; tosilizumab (Actemra), IL-6 reseptör antagonisti monoklonal antikor olup, romatoid artrit tedavisi ve sitokin salıverilmesi sendromlarında kullanılması için FDA onaylıdır. Makrofaj Aktivasyonu Sendromunun (MAS) sitokin fırtınası durumunda ve şiddetli pnömonili COVID-19' lu hastaların erken döneminde başarı göstermiştir. ARDS ve çok daha eskiden beri bilinen sepsis seyrinde antisitokin tedavilerinin yararlı olabileceğine dair kesin bir veri bulunmamakta ve bu ilaçlar rutin tedavide kullanılmamaktadır. ARDS'ye neden olabileceğine dair veriler de mevcuttur. Günde 400 mg' lık tek dozu ile hastaların %91' inde özellikle solunum fonksiyonlarında hızlı savunma mekanizmaları oluşmasında, yatan hastaların hızlı taburcu olmasında katkı sağlamıştır (55). Tosilizumab tek başına kullanılabildiği gibi kombinasyonlarla da kullanılabilmektedir. Tosilizumab gebelik, nötropeni, aktif tüberküloz, aktif hepatit B veya C, alerji, hipersensitivite varlığında kullanılmamalı, karaciğer fonksiyonları ve trombosit sayısı izlenmeli, divertikülit öyküsü olan hastalar gastrointestinal perforasyon açısından yakından izlenmelidir (2). Anakinra ise IL-1 blokajı yaparken, ciddi seyirli COVID-19 hastalığındaki etkinliği kontrollü klinik çalışmalarla araştırılmaktadır. MAS bulguları gelişen hastalarda, temin edilebildiğinde anakinra (rekombinant IL-1 reseptör antagonisti, kineret 100 mg hazır enjektör) tedavisi de güvenli bir seçenektir. Kısa yarı ömrü (4-6 saat) ve ihtiyaca göre doz (2-10 mg/kg) ve uygulama yolunu (deri altı ya da intravenöz) ayarlama avantajları daha güvenli bir tedavi olanağı sunabilir. CRP sentezini engellemediğinden, anakinra tedavisi alan hastalarda CRP düzeyleri, akut faz yanıtını takipte güvenli bir test olarak kullanılabilir (53). Sarilumab da romatoid artrit için onaylı diğer bir IL-6 reseptör antagonistidir. Şiddetli pnömonili COVID-19'lu hastalar için çalışmalar devam etmektedir Bevasizumab (antivasküler endoteliyal büyüme faktörü), fingolimod (Multipl sklerozis için onaylı immunmodulatör) ve ekulizumab ile ilgili çalışmalar devam etmektedir. Ekulizumab, sitokin salınımı ve endotel hasarı ile ilişkili TTP benzeri trombotik mikroanjiyopatide C5a inhibitörü olarak etki gösterir (2). JAK inhibitörleri de (ruksolitinib ve diğerleri), antisitokin tedavilerin yetersiz olduğu durumlarda kullanılabilir. Sonuç olarak, tosilizumab, anakinra, sarilumab gibi antisitokin tedaviler, MAS klinik ve laboratuvar bulguları gelişen COVID-19 hastalarında, kontrolsüz enflamasyonu baskılamak amacıyla dikkatli bir şekilde kullanılabilir.

İmmunoglobulinler

Hiperimmün immunoglobilinler ve iyileşen hasta plazmasının kullanılması diğer bir yardımcı tedavi olarak düşünülmektedir (56). Enfekte olup en az 28 gün önce iyileşen hastalardan antikorları alınarak tedavide kullanılabilir. SARS ve MERS tedavilerinde de kullanılmışlardır (57, 58). 2009' da yapılan H1N1' li 93 hastada yüksek ve düşük riskli hastalar karşılaştırıldığında mortalitede belirgin azaltma oluşturmuşlardır (59). Ancak COVID 19 çalışmaları yapıldıkça hastalığı geçirmiş bireylerinde IgG lerinin hızla negatifleştiği, hastalığı geçirmiş olmanın bireyleri uzun süreli olarak bağışıklamadığı yönündedir. Böylece iyileşen hasta plazması kullanımı da bir çözüm gibi görünmemektedir. Bu nedenlerle ancak vireminin pik yaptığı, primer immün yanıtın henüz oluşmadığı hastalığın ilk 7-10 günü içinde ve gün aşırı 3 dozda kullanılması ile etkili olduğu gözlenmektetir. Yapılan bir çalışmada da 0,3-0,5 g/kg dozda 5 gün iv kullanılan hastalarda başarılı sonuçlar alınmıştır (60).

Koagülopati Tedavisinde Kullanılan İlaçlar

COVID-19 hastalığı sırasında ayrıca tromboembolik olay gelişimi de sıkça gözlenmektetir. Hatta DİC (Dissemine intravasküler koagulopati) gelişmesi sonucu sepsisle hastalar hayatını kaybetmektedir. Virüsün ACE 2' ye bağlanması ile doğrudan endotel hasarı oluşturması, sepsiste gözlenen vasküler mikrotrombotik olay ile hareketsiz kalma, hastanede yatma ilişkili olarak koagülopati oluşmaktadır. Koagülopati gelişen hastalarda ise ölümlerin arttığı görülmüştür. Tüm COVID-19 hastalarına heparin profilaksisi uygulanmalıdır. İnflamasyon bulguları geçene kadar heparin profilaksi devamı önerilir. Düşük molekül ağırlıklı heparin olan Enoksaparin subkutan olarak yüksek dozda kullanımı önerilir (61). Antiinflamatuar ve antiagregan olarak dipiridamol (DIP) ile alakalı olarak yapılan bir çalışmada DIP verilen hastalarda (150mg/gün) hiperkoagulopatiyi önlediği gösterilmiştir. DIP' n antiagregan ve antinflamatuar etkisinin yanı sıra fosfodiesteraz enzimini etkileyerek ve viral replikasyonunu önleyerek antiviral etkisi yapılan bir in vitro çalışmada gösterilmiştir (62). Respiratuar yetmezlik gelişmesi durumunda kanama riski göz önünde bulundurularak doku plazminojen aktivatörü (tPA) ve defibrotid tedavilerinin kullanımı konusunda tedavi önerileri de yer almaktadır. Ciddi ve ölümcül olgularda progresif inflamatuvar faktör fırtınası ve koagülasyon bozukluklarının görülmesi kardiyovasküler komplikasyonların önüne geçilmesi gerektiğini işaret etmektedir. Bu sebeple, aspirinin virüs replikasyonunu inhibe edici, antikoagülan, platelet agregasyonunu inhibe edici ve antiinflamatuvar etkilerinin olması sebebiyle akciğer hasarına karşı etki göstereceği belirtilmektedir. Aspirinin erken dönemde kullanımının ciddi olguların insidansını , hastanede yatış süresini ve kardiyovasküler semptomları azaltması beklenmektedir (63).

Azitromisin

COVID-19 nedeniyle yatış endikasyonu olan özellikle ağır pnömoni durumlarında kullanılan makrolid grubu bir antibiyotiktir. Evde izlenecek hastalarda ise hidroksiklorokinle beraber kullanımlarında kardiyotoksisite yapmaları nedeni ile azitromisin tercih edilmemelidir. Özelikle ileri yaşlı, kardiyak morbiditesi yüksek olan, QT' yi uzatan ilaçları kullanan ve elektrolit bozuklukları olan hastalarda risk daha yüksektir. Bu nedenle COVID-19 nedeniyle hidroksiklorokin ve azitromisin kombinasyonu başlanacak veya almakta olan hastalarda QT uzaması dolayısıyla ventriküler taşikardi açısından uyanık olunması hatta kardiyoloji konsültasyonu yapılarak karar verilmesi gereklidir. Tedaviye başlanıldığında, EKG çekilerek yakından izlenmeli, kardiyotoksik istenmeyen etki görülenlerde öncelikle azitromisin kesilmeli daha sonra hidroksiklorokinin önce dozu azaltılmalı, sorun devam ederse tamamen kesilmesi düşünülmelidir (64).

İlaç ilaç etkileşmesi ve tedavideki etkililiği için New York'ta COVID-19 tanısı ile hastaneye yatırılan hastalar arasında yapılan bir çalışma da, hidroksiklorokin, azitromisin veya her ikisi ile tedavi yapılan hastaların sonuçları; her iki tedaviyle karşılaştırıldığında, hastane içi mortaliteleri açısından anlamlı bir ilişki gösterilememiştir. Bununla birlikte, bu bulguların yorumlanması için vaka sayısının yeterli olmayabilir(65).

COVID-19 pandemisi ölüm nedenleri arasında hastalarda pnömoni gelişmesi oldukça sıktır. Ayrıca normal şartlarda da bireyler çeşitli hastalıkları nedeniyle ilaçlar kullanmaktadırlar. Burada COVID-19 un özellikle pnomoni geliştirmesini hızlandırması anlamında Antipsikotikler ve antidepresanlar, opioid analjezikler, antikolinerjik ilaçlar, gabapentinoidler, proton pompası inhibitörleri ve inhale kortikosteroidlerin katkısı olup, bu ilaçları kullanan hastalarda pnömoni riskini 1,2 ila 2,7 kat artırabildikleri gözlenmiştir (66). Özellikle yaşlı hastalar bu ilaçlardan bir veya birkaçını kullanıyor olabilir. Bu nedenlerle ilaç-ilaç etkileşmeleri ve farmakovijilans açısından uyanık olmak gerekmektedir.

2. Sonuç

COVID-19 pandemisi ile ilgili olarak birçok ilaç gerek proflaksi, gerekse tedavi sırasın da

kullanılarak yaşamı uzatma ve tedavi sürecini hızlandırmada denenmekle beraber henüz bilinen bir ilacı ve aşısı yoktur. Dünya Sağlık Örgütü ve ABD Ulusal Sağlık Enstitüsü tarafından yürütülen çalışmalar göstermektedir ki 100 den fazla ilacın denenmesine rağmen henüz COVID-19'u tedavi eden veya bundan koruyan bir ilaç keşfedilmemiştir. Kullanılan bazı ilaçlar bazı bulgularda iyileşme sağlamış olsa da COVID ölümlerini önleyememektedir. Aşı çalışmaları sonucunda EMA ve FDI tarafından onaylanan aşılar olsa da kısa ve uzun vadeli etkileri konusu net değildir. Aşı çalışmaları ilk günden beri hala hem ulusal hem de uluslararası merkezlerde hızla devam etmektedir.

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