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Owned by on behalf of the Director of University of Medical Sciences Kartal Dr. Lütfi Kırdar Health Practice and Research Center, İstanbul: Recep DEMİRHAN | Executive Editor: Recep DEMİRHAN | Publication Type: Periodical | Printed: Yıldırım Matbaacılık +90 212 629 80 37 | Printing Date: December 2023 | Circulation: 50

ISSN 2587-0998

www.scie.online

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Volume 34 Issue 4 Year 2023

ORIGINAL ARTICLES

CASE REPORT

SCIE DOI: 10.14744/scie.2023.80269
South. Clin. Ist. Euras. 2023;34(4):295-300
Original Article

Diagnostic Approach to Solitary Pulmonary Nodules Discussed in Multidisciplinary Lung Cancer Council

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Submitted: 27.07.2023
Revised: 14.11.2023
Accepted: 17.11.2023

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Keywords: Benign; malignant; solitary pulmonary nodule; surgery.

ABSTRACT

Objective: The primary goal in solitary pulmonary nodule (SPN) management is to distinguish malignant lesions from benign ones. In our study, we aimed to evaluate the follow-up results, malignancy rates, and risk factors for malignancy of SPNs, which were discussed in our multidisciplinary lung cancer council (MLCC) with suspicion of malignancy and decided for surgical treatment.

Methods: Cases that were decided for surgical diagnosis and treatment after evaluation in the council were included in our study, which was planned prospectively. Demographic features, nodulsize, radiological features, location, Positron Emission Tomography (PET) findings, whether bronchoscopy and endobronchial ultrasonography were performed and their results, duration of follow-up before surgery, interventions and their results made for diagnosis, surgical method performed, and the final diagnosis were recorded. Chi-square and Mann–Whitney U tests were used in statistical analysis.

Results: Of the 33 cases in our study, 10 (30.3%) were female and 23 (69.7%) were male; the average age was 60.2±7.9 (min:42;max:77) years. The average diameter of SPN was measured as 16.5±6.3 (min:7; max:30) mm. When looking at their locations, it was seen that 72.7% were located in the upper lobes. 75.8% of the nodules were solid in character, 39.4% had spiculated contours, and 33.3% had lobulated contours. There was no calcification in 87.9% of the nodules. In the PET computed tomography examination, the average SUVmax value of nodules was measured as 6.05±6.01 (min:0; max:22), and there was no FDG uptake in the mediastinal lymph nodes of 21 (63.6%) cases. Surgical intervention was decided in 27 (81.8%) cases without a diagnosis. The final diagnosis was malignancy in 69.7% of cases. A statistically significant correlation was found between the final diagnosis and the edge features of the nodule and the SUVmax value (p=0.021, p=0.048, respectively).

Conclusion: Since SPN can represent early-stage primary lung cancer, risk factors and radiological features for each patient in SPN management should be individually assessed, and decisions should be made with a multidisciplinary approach. The aim is to minimize the outcomes of over-investigation, including patient anxiety and cumulative radiation exposure, while identifying nodules representing early malignancy.

INTRODUCTION

Solitary Pulmonary Nodule (SPN) etiology includes both benign and malignant diseases. Granulomatous lesions and hamartomas are among the most common benign diseases, while primary lung cancer and metastases are the most common malignant diseases. Also, inflammatory diseases, vascular lesions, and congenital diseases can cause SPN.[1] The approach to SPN is of critical importance due to SPN being the precursor lesion of lung cancer and lung cancer being among the most common cancers.[2] In the USA, 150,000 SPN cases are reported annually, and the prevalence of SPN in screenings of individuals with high risk for lung cancer is determined to be 8–51%.[2,3] In another study, the prevalence of malignancy in patients with SPN was shown to vary between 2% and 23%.[4]

Various guidelines have established management algorithms for SPNs. Our primary goal is to differentiate malignant nodules from benign ones. Several patient characteristics have been defined as risk factors for pulmonary

malignancy. These include advanced age, female gender, history of smoking, family history of lung cancer, the patient's own history of previous cancer, and exposure to asbestos and radon.[5] To best assess the patient in SPN, a comprehensive history along with the patient's radiological features should be evaluated together.

When evaluating a SPN radiologically, some clues have been identified to assist in risk stratification. These include edge characteristics, nodule size, doubling time of the volume, location, density, and calcification. Typically, benign nodules have smooth-bordered edges, while malignant nodules have irregular, lobulated, spiculated contours.[6] The size of the nodule is positively associated with the risk of malignancy. Fleischner's advice on nodule size is to take the average of the long and short axis diameters.[7] While malignant nodules typically have a growth rate between 30 and 400 days, the doubling time of volume for lung cancer has been reported as an average of 139 days.[8] In terms of location, although the site of the SPN is not used as a criterion for malignancy on its own, the upper lobe location is associated with an increased risk of malignancy.[5] The probability of malignancy increases as the ground-glass content in SPN increases, but the likelihood of malignancy is lower for nodules with pure ground-glass opacity compared to semi-solid nodules.[5] Calcification patterns of nodules in radiological imaging can be helpful in determining whether the nodules are benign. While benign nodules typically show diffuse, central, layered, and popcorn calcification, malignant nodules more commonly show punctate and eccentric calcification.[9]

When patient and nodule characteristics in SPN are evaluated as a whole, it can be easier to estimate the risk of malignancy in the nodule. Clinicians can classify this risk qualitatively or use quantitative models. There are various risk analysis calculators, including the American College of Chest Physicians (ACCP), Mayo Clinic, Bayesian, Veteran Affairs, Brock University, and Herder models.[5] In these models, the likelihood of the nodule being malignant can be calculated as a percentage using the characteristics of the patient and the nodule. As a result of these calculations, treatment and follow-up plans can be made according to risk groups. The ACCP risk model is recommended in the Fleischner guide.[10] For patients in the low-risk group, tomographic follow-up is recommended at varying frequencies, depending on the structure and size of the nodule.[11] For patients in the high-risk group, if the patient is suitable for surgery, it is recommended to perform wedge resection primarily with video-assisted thoracoscopic surgery.[12]

A SPN can be a benign lesion that does not require surgical intervention, or it can be a primary lung cancer that achieves high survival rates with surgical treatment. Therefore, it is critically important to evaluate SPN cases in multidisciplinary lung councils with clinical, radiological, and risk factors on a patient basis. In our study, we aimed to evaluate the follow-up results, malignancy rates, and risk factors for malignancy of patients we discussed in the multidisciplinary lung council due to the risk of malignancy.

MATERIALS AND METHODS

Of the 33 patients who were diagnosed with SPN, discussed in the multi-disciplinary lung council due to the risk of malignancy, for whom we decided on surgical diagnosis and treatment, and who accepted to participate in the study, they were included in our study from December 2019 to December 2020. Our study is prospectively planned research. Based on the data obtained from literature reviews, the demographic characteristics of the cases, the size of the nodule, its radiological characteristics, its location, PET computed tomography (PET-CT) findings, whether bronchoscopy and EBUS were performed and their results, the preoperative follow-up period, the interventions performed for preoperative diagnosis and their results, the surgical method used, and the final diagnosis were recorded. Statistical analyzes were performed using the SPSS

19.0 (IBM Corporation, Armonk, NY, USA) package program. Chi-square and Mann–Whitney U tests were used. The study (No. 2023/514/254/22; Date: July 19, 2023) was approved by the ethics committee, and an informed consent form was obtained. It was conducted in accordance with the Declaration of Helsinki.

RESULTS

Of the 33 cases included in our study, 10 (30.3%) were female 23 (69.7%) were male; the average age was 60.2±7.9 (min:42; max:77) years. When patients were evaluated according to inclusion and exclusion criteria, patients with primary tumors were not included in the study. When we evaluated the characteristics of the nodule radiologically, the average diameter of the SPN was measured as 16.5±6.3 (min:7; max:30)mm. It was seen that the nodule diameter of 27 (81.8%) patients was 2 cm or less. When their locations were examined, it was found that 42.4% were in the right upper lobe, 30.3% were in the left upper lobe, and 72.7% were located in the upper lobes (Figure 1). When the nodules were evaluated according to their edge characteristics, 39.4% had spiculated contours, and 33.3% had lobulated contours. While 25 (75.8%) of the nodules had a solid component, 8 (24.2%) were semi-solid

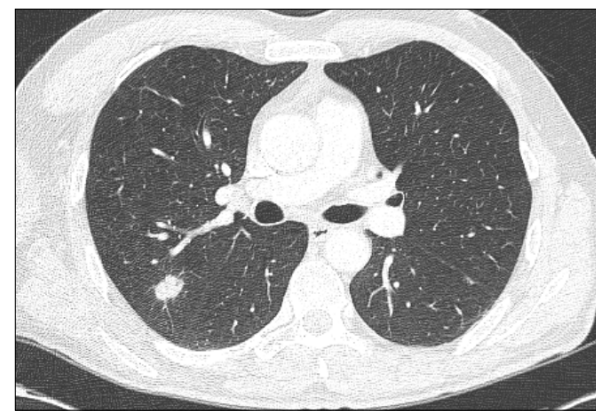

Figure 1. Right lung upper lobe posterior segment solid nodule.

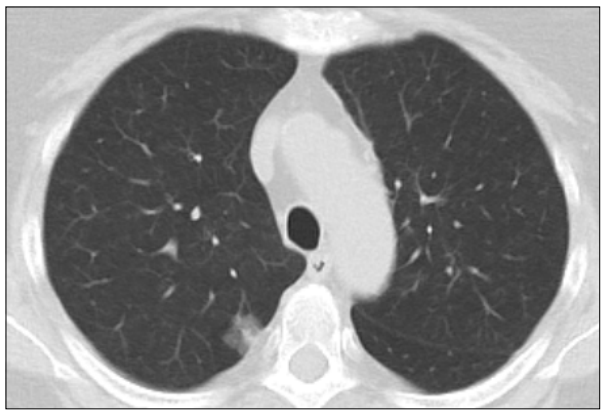

Figure 2. Right lung upper lobe posterior segment semisolid nodule.

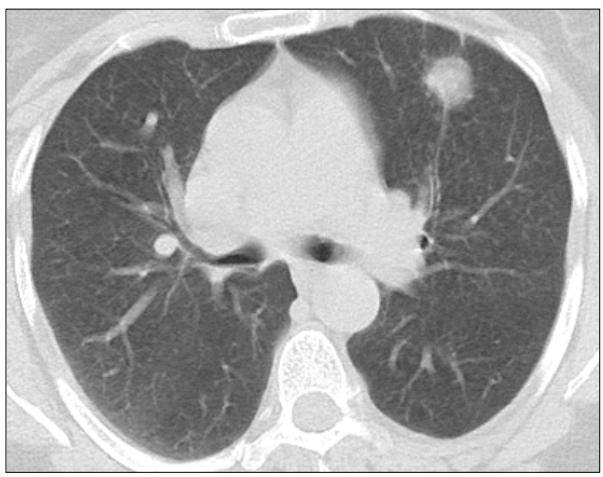

Figure 3. Left lung upper lobe lingular segment ground glass nodule.

(Figures 2 and 3). When evaluated according to whether they contained calcification, 89.9% of the nodules had no calcification. When looking at the follow-up periods from the initial diagnosis to surgical treatment of the nodules, it was calculated as an average of 1.52±3.6 (min:0; max:15) months. In the PET-CT examination, the average SUVmax value of the nodules was measured as 6.05±6.01 (min:0;-max: 22), and there was no FDG uptake in the mediastinal lymph nodes in 21(63.6%) cases. When the diagnostic tests performed on the patients were examined, 24 patients underwent video bronchoscopy, and 6 patients underwent transthoracic needle aspiration biopsy. EBUS was performed for diagnostic and staging purposes in patients with mediastinal lymph node involvement and in need of staging. Thus, malignant patients were staged along with their diagnosis. A surgical decision was made for 27 cases evaluated in our multidisciplinary lung council without diagnosis. While the final diagnosis was malignancy in 69.7% of the cases, it was benign in 30.3%. When the nodule characteristics of patients with malignant outcomes were examined, a statistically significant relationship was found between the edge of the nodule and malignancy (p=0.021). All nodules with spiculated contours and 81.8% of nodules with lobulated contours were malignant. At the same time, 56.5% of the malignant nodules had spiculated contours, 39.1% had lobulated contours, and 13.0% had smooth contours. There was also a statistically significant relationship between the SUVmax value of the nodule and the final diagnosis (p=0.048). The average SUVmax value of malignant nodules was 8.61, and the average SUVmax value of benign nodules was 3.5. No relationship was found between age, gender, nodule localization, presence of calcification, and structure of the nodule and the final diagnosis.

DISCUSSION

In our study, the final diagnosis was found to be malignancy in 23 (69.7%) of the 33 patients who were diagnosed with SPN, discussed in the multidisciplinary lung council with the suspicion of malignancy, and received a histopathological diagnosis. When the radiological characteristics of SPN were examined, a statistically significant relationship was found between the edge of the nodule and malignancy. There was also a statistically significant relationship between the SUVmax value of the nodule and the final diagnosis.

When literature data for cancer prevalence in SPN were examined, in a study conducted by Li et al.[13] at Wuhan Central Hospital in China involving 496 patients with histopathological diagnosis, it was found that 425 patients were diagnosed with malignant tumors and 71 patients were diagnosed with other non- malignant lung diseases. In a study involving 244 patients in the United Kingdom, it was shown that 99(40.6%) patients had malignant nodules.[14] In a study conducted by Sim et al.,[15] 85% of 186 patients with pathologically confirmed diagnosis were reported to be malignant, and 15% had benign pathology. In a study by Schultz et al.[16] involving 151 patients, the prevalence of malignancy was 44%. In a study conducted in the Netherlands involving 106 patients, it was shown that 61 patients (57%) had malignant nodules.[17] When the data of our country are examined, in a study conducted by Caylak et al.[18] involving 110 patients, 35% of the nodules were observed as malignant, and 65% were benign. There are different rates related to SPN malignancy prevalence in the literature. In our study, it was found that 69.7% (23 patient) of 33 patients with histopathologically confirmed SPN diagnosis had malignant nodules.

Evaluating the edge features of a nodule morphologically when assessing an SPN in risk classification is an important clue. In radiological imaging, a spiculated edge is a finding supporting malignancy.[19] The positive predictive value for malignancy is between 88 and 94%.[20] In the literature, nodules with spiculated edges are almost always defined as an indicator of malignancy in most of all studies.[19-23] The lobulated edge has also been shown to be the ultimate precursor of SPN malignancy in some studies.[6,23] Consistent with the literature data, our study found a statistically significant relationship between the edge characteristics of the nodule and malignancy.

Because cancer cells have high metabolic activity, positron emission tomography (PET-CT) is used in functional imaging to differentiate between benign and malignant diseases. PET-CT is recommended for nodules 8–10 mm and larger in diameter, and the possibility of malignancy increases in nodules with PET-CT uptake and a SUVmax value above 2.5.[24] In a retrospective study involving SPN patients, the sensitivity of PET-CT was evaluated at 97% and the specificity at 85%.[25] In a study by Yilmaz et al.[26] involving 241 patients, when average SUVmax values were compared according to nodule diameter, the average SUVmax value of the patients was found to be significantly higher in patients with nodule diameter ≥1 cm, and the average SUVmax value of malignant nodules was significantly higher. In our study, a statistically significant relationship was found between the SUVmax value of the nodule and malignancy. The average SUVmax value of the nodules was measured as 6.05±6.01 (min:0; max:22). When mediastinal lymph nodes were evaluated with PET-CT, there was no FDG uptake in the mediastinal lymph nodes of 21 (63.6%) cases.

In SPN, the risk of malignancy increases as the nodule size increases. Nodule size is an independent indicator of malignancy risk. More than 80% of benign nodules have a diameter <2 cm. However, 15% of malignant nodules have a diameter <1 cm, and 42% have a diameter <2 cm.[27] Numerous studies have shown that as nodule size increases, the risk of malignancy increases.[5,7,21-23] In our study, the average diameter of the nodules was measured as 16.5±6.3 (min:7; max:30) mm, and no significant relationship was shown between nodule size and malignancy. When the nodule sizes of the patients were examined, it was seen that the nodule diameter of 27(81.8%) patients was 2 cm or below. Twenty of these patients had a malignant diagnosis. At the same time, 69.7% of all patients in our study had histopathological malignancies. This situation shows us the importance of diagnostic biopsy for smaller-sized SPNs as well.

According to the Fleischner guide, the upper lobe location of the nodule and suspicious morphology increase the risk of malignancy.[7] In a study conducted by McWilliams et al.,[5] the upper lobe location of the nodule was shown to be associated with an increased risk of malignancy. In a study conducted by Swensen et al.,[21] the upper lobe location was determined as an independent determinant of malignancy. In our study, when the locations were examined, 42.4% were in the right upper lobe, 30.3% were in the left upper lobe, and 72.7% were located in the upper lobes, but no significant relationship was found between localization and malignancy. Regarding the density of the nodule, according to the Fleischner guide, the malignancy rate of semisolid nodules is higher than that of solid nodules. The studies conducted also support this situation.[5] However, in our study, no significant relationship was shown between malignancy and nodule structure.

In SPN, the presence and pattern of calcification are parameters evaluated in the differentiation of benign and malignant diseases.[9] In a study conducted by Toomeset al.,[28] 92% of calcified SPNs were benign. In a study conducted by Yilmaz et al.,[26] similar to these data, it was shown that the average SUVmax value in calcified SPN was lower than non-calcified ones. In our study, however, 89.9% of the nodules had no calcification, and no significant relationship was found between malignancy and calcification.

Several guidelines have been developed for SPN follow-up. The Fleischner Society guideline suggests a CT follow-up after 3 months, a PET-CT scan, and/or biopsy for solid nodules larger than 8 mm in high-risk patients. For ground-glass nodules larger than 6 mm, they recommend a CT follow-up every 6–12 months, followed by a CT follow-up every 2 years up to 5 years. For semisolid nodules larger than 6 mm, they recommend a CT follow-up every 3–6 months, followed by an annual CT follow-up up to 5 years.[7] The ACCP 2013 guideline suggests tissue diagnosis if growth is observed during the follow-up of a nodule smaller than one centimeter and a candidate for surgery.[28] In our study, when we looked at the follow-up periods from the initial diagnosis of the nodules to the surgical procedure, it was determined to be an average of 1.52±3.6 (min:0; max:15) months. We see that the follow-up time in our study is shorter than the guidelines' recommendations. When we look at the histopathological diagnoses of the nodules, the fact that a high rate like 69.7% is of malignant character suggests that a definitive judgment cannot be made without a tissue diagnosis, even though important approaches are obtained with various models to determine the risk of malignancy of the nodule. In a study conducted among pulmonologists, chest surgeons, and radiologists in SPN follow-up, a survey study was conducted on the same cases with specialist doctors, and the preferred treatment approach was evaluated. Significant differences were observed in the treatment approach in all three specializations.[29] This situation suggests the importance of discussing the cases in multidisciplinary councils attended by pulmonology, chest surgery, radiology, medical oncology, and radiation oncology.

Conclusion

In conclusion, with this study, the follow-up results of SPNs discussed in the multidisciplinary lung council, malignancy rates, and risk factors for malignancy have been evaluated. The approach to SPN is critically important on one hand due to the possibility of achieving a cure with surgical resection for primary lung cancer and, on the other hand, because of the possibility of a benign nodule being directed to surgery with an aggressive approach. The aim is to minimize the outcomes of over-investigation, including patient anxiety and cumulative radiation exposure, while identifying nodules representing early malignancy. At this stage, the patient's preferences can also guide the decision. The situation can be discussed in detail with the patient, and a joint decision can be made while staying true to medical terminology. For nodules carrying a high risk of malignancy, histopathological verification at this stage can provide a chance for cure in diagnosed lung cancers, while a conservative approach favoring waiting can rob the

patient of their chance for a cure. Although various algorithms are used to determine the risk of malignancy of the nodule, a definitive judgment cannot be made without a tissue diagnosis. In SPN management, risk factors and radiological characteristics for each patient should be evaluated individually, and decisions should be made with a multidisciplinary approach.

Limitations

The study's limitations include being a single-center study and having a limited sample size. Also, the study being based on a population referred for biopsy or surgery can lead to selection bias.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 19.07.2023, Decision No: 2023/514/254/22).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Ş.C., R.D.; Design: S.Ş.C., R.D.; Supervision: S.Ş.C., R.D.; Fundings: E.E.G., H.Ç.E.; Materials: E.E.G., K.B.Ö.; Data: H.Ç.E., E.E.G.; Analysis: N.K., K.B.Ö.; Literature search: H.Ç.E., N.K.; Writing: H.Ç.E.; Critical revision: H.Ç.E., K.B.Ö., N.K.

Conflict of Interest

None declared.

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Multidisipliner Toraks Konseyinde Tartışılan Soliter Pulmoner Nodüllere Tanısal Yaklaşım

Amaç: Soliter akciğer nodülü (SPN) yönetiminde ana hedef malign lezyonları benign lezyonlardan ayırabilmektir. Çalışmamızda malignite şüphesiyle multidisipliner akciğer kanseri konseyimizde (MAKK) tartışılan ve cerrahi tedavi kararı verilen SPN'lerin izlem sonuçları, malignite oranları ve malignite için risk faktörlerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Prospektif olarak planlanan çalışmamıza MAKK'ye cerrahi girişim önerisi ile çıkardığımız ve konseyde değerlendirerek cerrahi tanı ve tedavi kararı verdiğimiz olgular dahil edildi. Olguların demografik özellikleri, nodül boyutu, radyolojik özellikleri, yerleşimi, Pozitron Emisyon Tomografisi bulguları, bronkoskopi ve endobronşial ultrasonografi yapılıp yapılmadığı ve sonuçları, cerrahi öncesi takip süresi, tanı için yapılan girişimler ve sonuçları, yapılan cerrahi metodu ve final tanı kayıt altına alındı.

Bulgular: Çalışmamızdaki 33 olgunun 10'u (%30.3) kadın, 23'ü (%69.7) erkek; yaş ortalamaları 60.2±7.9 (min: 42; maks: 77) yıl idi. SPN'nin ortalama çapı 16.5±6.3 (min: 7; maks: 30) mm ölçüldü. Yerleşimlerine bakıldığında %72.7'sinin üst loblarda yerleştiği görüldü. Nodüllerin %75.8'i solid özellikte olup, %39.4'ü spiküler konturlu, %33.3'ü lobüle konturlu idi. Nodüllerin %87.9'unda kalsifikasyon yoktu. PET-CT incelemesinde nodüllerin ortalama SUVmaks değeri 6.05±6.01 (min: 0; maks: 22) olarak ölçüldü ve 21 (%63.6) olgunun mediastinal lenf bezlerinde FDG tutulumu yoktu. 27 (%81.8) olguya tanısız olarak cerrahi girişim kararı verilmişti. Olguların %69.7'sinde final tanı malignite idi. Final tanı ile nodülün kenar özellikleri ve SUVmaks değeri arasında istatistiksel olarak anlamlı bir ilişki saptandı (p=0.021, p=0.048).

Sonuç: SPN erken evre primer akciğer kanserini temsil edebileceğinden SPN yönetiminde her hasta için risk faktörleri ve radyolojik özellikleri bireysel olarak değerlendirilmeli ve multidisipliner yaklaşımla karar alınmalıdır. Amaç, erken maligniteyi temsil eden nodülleri tespit ederken, hasta kaygısı ve kümülatif radyasyon maruziyeti dahil olmak üzere aşırı incelemenin sonuçlarını en aza indirmektir.

Anahtar Sözcükler: Benign; cerrah; malign; soliter pulmoner nodül.

SCIE DOI: 10.14744/scie.2023.59480
South. Clin. Ist. Euras. 2023;34(4):301-305

Original Article

Evaluation of Clinical and Radiological Results of the Perioperative and Postoperative Periods in the Endovascular Treatment of Vertebral Artery Stenosis

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Submitted: 21.08.2023
Revised: 07.12.2023
Accepted: 07.12.2023

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Keywords: Complication; symptomatic vertebral artery stenosis; stenting.

ABSTRACT

Objective: The purpose of this study was to showcase the outcomes of endovascular treatment, assessing its safety and efficacy for patients with symptomatic severe atherosclerotic stenosis of the vertebral artery, who did not respond to medical management and were treated at our institution.

Methods: We performed a retrospective analysis on patients who had suffered a transient ischemic attack or ischemic stroke and received endovascular treatment for symptomatic vertebral stenosis despite being under medical care. The endovascular techniques utilized were cataloged as angioplasty alone, balloon-mounted stenting, or angioplasty with subsequent self-expanding stent insertion. We recorded both peri-procedural complications, such as in-stent thrombosis, dissection, and guide wire perforation, as well as post-procedural complications, including stroke and transient ischemic attack. The study focused on analyzing the endovascular treatment methodologies alongside clinical and radiological outcomes.

Results: From January 2020 to December 2022, 15 patients were treated, including 6 with V1 segment stenosis, 2 with V2, and 7 with V4 segment stenosis. The rate of successful stent placement was 100% (15 out of 15). Six patients (40%) received a balloon-expandable stent in addition to angioplasty, while the remaining nine (60%) were treated with a self-expanding stent following angioplasty. No peri-procedural complications were reported in patients who had extracranial stenting. However, during intracranial stenting, complications occurred in two cases: one patient had a dissection leading to occlusion of a perforator artery, and another experienced stent thrombosis. These complications resulted in ischemic strokes and subsequent mortality during hospitalization in two patients (13% of the cohort). The median follow-up duration was 15 months, with an interquartile range of 9 to 24 months. An improvement in the modified Rankin Score was noted in 10 patients, while no change was observed in 3 patients.

Conclusion: Our findings advocate for the safety and probable efficacy of endovascular treatment in patients with vertebral artery stenosis who are non-responsive to optimal medical therapies. Stenting, particularly for extracranial vertebral artery stenosis, can be performed with a low rate of complications and is deemed safe.

INTRODUCTION

Posterior circulation strokes account for approximately 20% of all ischemic strokes. Atherosclerosis of the posterior circulation arteries is also responsible for 25% of these strokes.[1,2] The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study showed that stroke rates at the same site as the stenotic artery were 10.7% in patients with basilar artery stenosis and 7.8% in patients with vertebral artery (VA) stenosis, with a twofold increase in stroke risk in patients with stenosis >70%.[1,2,3]

Treatment of symptomatic VA stenosis includes medical, surgical, and endovascular treatments. The stenosis site of the VA is mostly proximal to the artery. Surgical intervention on the VA in this region is technically challenging due to limited access to the vascular origin, thus it is often considered an unfeasible option.

Endovascular treatment (ET) of the VA stenosis comprises percutaneous transluminal angioplasty with or without stent deployment. Well-known international studies have demonstrated that stenting for symptomatic carotid stenosis can be effective in selected patients. However, the most effective approach to managing individuals with symptomatic VA stenosis has not yet been determined.

In patients with severe vertebral artery stenosis, despite standard medical treatments including antiplatelet agents and statins, the risk of recurrent stroke within 90 days may increase up to 33%.[4] Hence, aggressive treatment is of significant importance in the prognosis of patients. On the other hand, endovascular treatments are hopeful methods in these patients who do not respond to the best medical therapy (BMT). However, appropriate patient selection is important because of outcomes such as procedural stroke, intracranial hemorrhage, and death. In studies involving case series, it has been demonstrated that angioplasty and/or stenting can be effective treatment options in VA stenosis, and stenting has very low complication rates of 1-1.5%, particularly for Extracranial VA stenosis. This rate has been reported to be approximately 7-10% in intracranial vertebral artery stenosis. While examining randomized controlled trials, it is noteworthy that a clear consensus has not been reached.[2,4]

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study has reported worse outcomes for stenting compared to BMT in patients with stenosis in various intracranial cerebral arteries. The Vertebral Artery Stenting Trial (VAST) study, which included patients with intracranial and extracranial VA stenosis, found no significant difference between stenting and BMT.[2-4] However, the Vertebral Artery Ischaemia Stenting Trial (VIST) study concluded that stenting is effective and reliable, particularly in cases of extracranial vertebral artery stenosis. The variability in study outcomes can be attributed to several factors such as differences in the location and severity of stenosis, variations in devices and procedural techniques employed, and the level of experience of the operators.[2-4]

The aim of our study was to share the perioperative and postoperative outcomes, complication management, clinical and radiological results of patients who underwent endovascular treatment due to severe extra and intracranial vertebral stenosis.[2,5,6]

MATERIALS AND METHODS

This study was conducted prospectively and analyzed retrospectively between January 2020 and December 2022. Patients aged 18–85 who exhibited symptoms of transient ischemic attack (TIA) or mild stroke in the posterior circulation and had a 70% or greater degree of stenosis in the vertebral artery due to atherosclerotic disease were included in the study consecutively. Other inclusion criteria involved a recent non-disabling stroke or TIA that occurred within 90 days in the VA vascular territory, refractory to standard medical therapy, and stroke or TIA recurrence due to severe stenosis of the VA under intensive risk factor control, such as hypertension and diabetes mellitus. The symptomatic duration was determined as 3 months, based on data indicating the highest stroke risk within this period.

Exclusion criteria included:[1] VA artery stenosis caused by dissection;[2] non-atherosclerotic stenosis;[3] known contraindications to heparin, aspirin, clopidogrel, anesthesia, and contrast agents;[4] pregnancy and lactation in women;[5] a life expectancy of less than 1 year due to other medical conditions. The study was approved by the institutional ethics committee on 19/07/2023. The study procedure was conducted in accordance with the Declaration of Helsinki and regulations for human studies.

Management of risk factors, antiplatelet therapy, and lipid-lowering therapy formed the basis of medical treatment, with individual treatments for comorbidities such as hypertension or diabetes also being important. The recommended antiplatelet therapy for the procedure was a combination of clopidogrel and acetylsalicylic acid. If not already on dual therapy, a loading dose of 300-600 mg of clopidogrel was administered at least 12 hours before the procedure. Resistance to acetylsalicylic acid and clopidogrel was assessed in all patients prior to the procedure.

Endovascular treatment (ET) options included angioplasty alone, the placement of a balloon-mounted stent, and the placement of a self-expanding stent with angioplasty. Clinical complications such as stroke, transient ischemic attack (TIA), and mortality were recorded following the procedures.

The primary outcome was the occurrence of ischemic or hemorrhagic stroke, TIA, or death related to the endovascular procedure during hospitalization. The secondary outcome included successful revascularization (residual stenosis <30%) and periprocedural complications such as vessel dissection, stent dislocation, or acute stent occlusion noted on the 90th day following stenting.

The primary safety outcome encompassed a combination of stroke within 30 days post-randomization, TIA in any region between 2 and 30 days, all-cause mortality within the first 30 days post-procedure, and intracranial hemorrhage within 30 days post-randomization.

Dual antiplatelet therapy was continued for a minimum of 3 months following ET. Clinical evaluation was performed by two independent interventional neurologists who assessed the patients immediately before treatment, at discharge, and at 3 months.

The National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) were used for assessment. Stenosis was gauged based on the distal normal vessel diameter as defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Statistical Analysis

Continuous variables were expressed as median and in-

Table 1. Patient clinical and technical results

Case	Clinical before procedure	Age/Sex	Vessel	Contralateral stenosis or occlusion	Stenosis before procedure (%)	Restenosis	Stent	Diameter (mm)	Intervention method	MRS before	MRS in 3 months
1	Stroke	70/M	V1	YES	85	0	CS	3.5	Balloon mounted stent	1	0
2	Stroke	67/M	V1	YES	95	0	CS	3.0	Balloon mounted stent	1	0
3	Stroke	69/M	V1	YES	70	0	CS	3.5	Balloon mounted stent	3	1
4	Stroke	68/M	V1	YES	90	0	CS	4.0	Balloon mounted stent	3	1
5	Stroke	67/M	V1	NO	80	0	CS	3.5	Balloon mounted stent	2	0
6	TIA	80/M	V1	YES	85	0	CS	3.0	Balloon mounted stent	0	0
7	Stroke	49/M	V2	YES	90	0	ICS	4	Self-expending stent	3	1
8	TIA	79/M	V2	YES	80	0	ICS	4	Self-expending stent	0	0
9	Stroke	68/F	V4	YES	80	1	ICS	4	Self-expending stent	1	0
10	Stroke	43/M	V4	YES	90	0	ICS	4	Self-expending stent	6	6
11	Stroke	51/M	V4	YES	75	0	ICS	4	Self-expending stent	6	6
12	Stroke	54/M	V4	YES	95	0	ICS	4	Self-expending stent	0	0
13	Stroke	71/M	V4	YES	80	0	ICS	3	Self-expending stent	3	1
14	Stroke	67/M	V4	YES	90	0	ICS	4	Self-expending stent	1	0
15	Stroke	72/M	V4	YES	80	0	ICS	4	Self-expending stent	2	0

CS: Coronary stent (Alvimedica); ICS: Intracranial stent (Neuroform Atlas, Stryker, California, USA); TIA: Transient ischemic attack.

terquartile range (IQR), and categorical variables as n (%). Statistical analyses were performed using IBM SPSS Statistics Software version 21 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 15 patients who experienced a stroke or TIA due to VAS, 14 were male with a median age of 68 years (IQR 60.5–70.5). Of the 9 patients with extracranial VAS stenosis, 7 were located in the V1 segment, 2 in the V2 segment, and all 6 intracranial stenoses were in the V4 segment. Patient data, along with clinical and technical results, are summarized in Table 1.

The rate of successful stent deployment was 100% (15/15). The overall complication rate, considering all adverse events, was 13% (2/15). Complications included one case of dissection following balloon angioplasty during the procedure (Case 10), and one instance of stent thrombosis (Case 11), both occurring in patients with V4 segment stenosis. Within 24 hours post-procedure, two ischemic events were noted: one related to stent thrombosis and the other to perforator injury subsequent to dissection. The patient with stent thrombosis suffered extensive ischemia involving the pons and medulla oblongata and succumbed to bulbar ischemia, while the patient with perforator injury also died during hospitalization.

Balloon-mounted stents were utilized in 6 patients with V1 stenosis (6/6, 100%), and self-expanding stents were used in all patients with V2 (2/2, 100%) and V4 stenosis (7/7, 100%) (Figure 1 and Figure 2). In one instance of V4 stenosis (Case 9), a restenosis rate of 60% was observed, yet retreatment was not deemed necessary during follow-

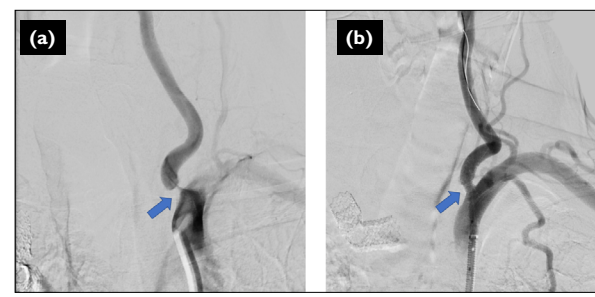

Figure 1. Angiographic Imaging Findings of a Patient with Proximal Vertebral Artery Stenosis Before and After Treatment, **(a)** Preprocedural left subclavian artery angiography from the frontal oblique view reveals high-grade ostial stenosis in the left vertebral artery (indicated by a blue arrow). **(b)** Postprocedural control angiography following primary stent placement with a balloon-mounted stent shows adequate restoration of the vessel lumen.

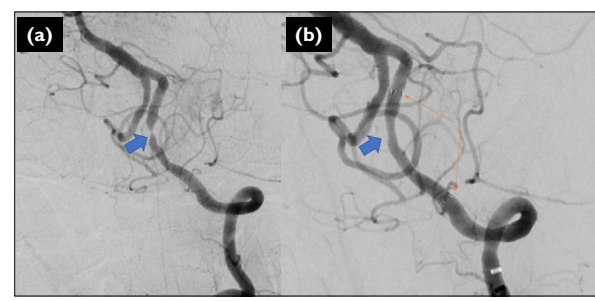

Figure 2. Angiographic Imaging Findings of a Patient with Distal Vertebral Artery Stenosis Before and After Treatment **(a)** Preprocedural intracranial angiogram of the left vertebral artery in the anterior view displays high-grade distal V4 stenosis. **(b)** Postprocedural control angiography illustrates significant improvement in the distal V4 stenosis of the vertebral artery (highlighted by a blue arrow). The proximal and distal ends of the stent are denoted by orange arrows.

up. Two patients who underwent self-expanding stenting for V4 stenosis experienced complications related to the interventional technique (2/7, 29%), one of which was dissection due to balloon angioplasty.

For patients who survived, the median follow-up duration was recorded as 15 months (IQR 9–24). During post-treatment follow-up, these patients did not develop new infarcts nor did they exhibit any worsening in NIHSS scores. The mRS scores of the 13 surviving patients showed improvement over the three-month follow-up period.

DISCUSSION

The clinical and treatment processes related to extracranial and intracranial segment stenosis of the vertebral artery differ. VA stenosis most commonly occurs at the orifice, specifically in the V1 segment, which is why there is more experience and research on extracranial vertebral artery stenosis. Stenting for extracranial VA stenosis demonstrates a 1% complication rate. In our study, none of the 8 patients with extracranial VA stenosis developed major or minor complications.[2,7,8]

The technical failure rate for endovascular treatment of vertebral artery extracranial segments is generally low.[9] Challenges are more likely in patients with anatomical complexities, such as those with a type 3 aortic arch or tortuous subclavian artery. Both intracranial and extracranial interventions have been shown to be effective.[9]

Percutaneous transluminal angioplasty (PTA) was the initial endovascular procedure of choice for treating vertebral artery stenosis.[9] However, high restenosis rates post-PTA have been reported. Cloud et al.[10] found restenosis rates of up to 100% in patients treated with balloon angioplasty alone. Stayman et al.[3] reported nearly identical rates of TIA and stroke at 0.8% and 1.1%, respectively, in 993 patients who underwent PTA and stenting, leading to a preference for combining stenting with PTA.[9,10] We applied both PTA and stenting to all our patients.

For extracranial VAS treatment, pre-dilation with a smaller balloon catheter than the lesion followed by stenting is common. The stent choice depends on the vertebral artery's diameter, ranging from 3 to 6 mm. Coronary stents are suitable for VA in terms of diameter and flexibility, but their radial force is not optimal. They are preferred for short segment stenosis like orifice lesions.[9,11] In our patients with V1 stenosis, we initially performed PTA, followed by placement of a balloon-expandable coronary stent.

Due to the vertebrobasilar junction, basilar artery stenosis and V4 segment stenosis are frequently observed simultaneously, presenting higher risks of morbidity and mortality. However, variability in these rates exists across studies due to factors such as sample size, stenosis severity, presence of contralateral stenosis, endovascular technique, and operator experience. For instance, the SAMMPRIS and VISSIT trials showed primary outcome rates of 14.7% and 24.1% within 30 days.[2] A comprehensive meta-analysis covering 23 studies indicated a stroke recurrence or death risk of 8.9 per 100 person-years in the endovascular group.[9,10] In our study, stroke and mortality were observed in two hospitalized patients.

Intracranial arteries are more vulnerable as they contain fewer elastic fibers, traverse the subarachnoid space, and lack surrounding protective tissue. Hence, vessel rupture or perforation may occur during intracranial PTSA due to microwire manipulation or excessive balloon inflation. The risk of vessel rupture significantly increases with rapid balloon inflation or use of unsuitably sized balloons or stents.[12,13] One of our intracranial cases experienced an ischemic event following PTSA due to dissection and related perforator artery occlusion.

In-stent restenosis is another potential complication. Factors such as stent type, initial vertebral artery segment tortuosity, atherosclerotic lesion length, smoking, and diabetes can elevate restenosis rates. A meta-analysis of 9 non-randomized studies showed significantly lower restenosis rates (8.2%) with drug-eluting stents (DES) compared to bare-metal stents (BMS) (23.7%).[9] Additionally, a direct correlation between restenosis and recurrence of VBI symptoms has not been established. Patients with restenosis often remain asymptomatic during follow-up.[14] After a median follow-up of 2.5 years, VA stenting was shown to provide lasting symptomatic relief in roughly 70% of patients. No recurrent symptoms or complaints were reported by our patients during a 15-month follow-up period.[15] Significant improvement in mRS scores was observed post-procedure and at the 3-month follow-up.

Conclusion

Current literature has not yet proven the superiority of endovascular therapy over medical therapy. With optimal medical management, angioplasty and stenting might be a safe approach for managing recurrent strokes in extracranial vertebral artery stenosis. In cases of intracranial vertebral artery stenosis, patient selection should be particularly cautious, especially due to the risk of perforator artery occlusions.

Ethics Committee Approval

This study approved by the Dr. Lutfi Kırdar City Hospital Ethics Committee (Date: 19.07.2023, Decision No: 2023/5141254/30).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.G., A.O.; Design: E.G., A.O.; Supervision: E.G.; Fundings: A.O.; Materials: A.O.; Data: A.O.; Analysis: E.G., A.O; Literature search: E.G., A.O; Writing: A.O.; Critical revision: E.G.

Conflict of Interest

None declared.

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Vertebral Arter Stenozlarının Endovasküler Tedavisinde Perioperatif ve Postoperatif Dönem Klinik ve Radyolojik Sonuçlarının Değerlendirilmesi

Amaç: Bu çalışmanın amacı, merkezimize başvuran ve medikal tedaviye yanıt vermeyen, semptomatik ciddi aterosklerotik vertebral arter hastalığı olan hastalarda endovasküler tedavinin sonuçlarını sunmak, güvenliliğini ve etkinliğini araştırmaktır.

Gereç ve Yöntem: Medikal tedavi altında geçici iskemik atak veya iskemik inme geçiren, semptomatik vertebral arter stenozuna bağlı endovasküler tedavi uygulanan hastalar geriye dönük olarak analiz edildi. Uygulanan endovasküler yöntemler tek başına anjiyoplasti, balona monteli stentleme ve anjiyoplasti ardından kendiliğinden genişleyen stent yerleştirilmesi olarak kaydedildi. İşlem sırasında stent içi tromboz, diseksiyon, kılavuz tel perforasyonu gibi perioperatif komplikasyonlar ve inme, geçici iskemik atak gibi işlem sonrası komplikasyonlar kaydedildi. Endovasküler tedavi yöntemleri, klinik ve radyolojik sonuçlar analiz edildi.

Bulgular: Ocak 2020-Aralık 2022 tarihleri arasında V1 darlığı olan 6 hasta, V2 darlığı olan 2 hasta ve V4 darlığı olan 7 hasta olmak üzere toplam 15 hastaya endovasküler tedavi uygulandı. Başarılı stent yerleştirme oranı %100'dü (15/15). Bu hastaların 6'sına (%40) balon anjioplasti ardından balonla genişleyen stent, geri kalan 9 (%60) hastaya ise balon anjıoplasti ardından kendiliğinden genişleyen stent uygulandı. Ekstrakranial stent uygulanan hastaların hiçbirinde periprosedürel komplikasyon görülmedi. İntrakraniyal stentleme sırasında, bir hastada perforatör arterde diseksiyon ve bunun sonucunda tıkanma görülürken, başka bir hastada stent trombozu gelişti. Bu iki hastada komplikasyonlara bağlı iskemik inme gelişti ve hastanede yatış sırasında mortalite görüldü (2/15, %13). Hastaların ortanca takip süresi 15 aydı (çeyrekler arası aralık, 9-24). Modifiye Rankin Skorunda (mRS) 10 hastada iyileşme gözlenirken, 3 hastada değişiklik görülmedi.

Sonuç: Bu çalışma, optimal tıbbi tedaviye dirençli vertebral arter stenozu olan hastalarda endovasküler tedavinin güvenliğini ve potansiyel etkinliğini desteklemektedir. Özellikle ekstrakranial vertebral arter darlıklarında stentleme işlemi düşük komplikasyon oranları ile uygulanabilinir.

Anahtar Sözcükler: Komplikasyon; semptomatik vertebral arter stenozu; stentleme.

SCIE DOI: 10.14744/scie.2023.24445
South. Clin. Ist. Euras. 2023;34(4):306-311

Original Article

The Effect of Gliclazide use on BDNF and NGF Levels in Rats with Diabetes Mellitus

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Submitted: 02.05.2023
Revised: 19.06.2023
Accepted: 20.07.2023

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Keywords: Brain-derived neurotrophic factor; gliclazide; nerve growth factor; neurodegeneration.

ABSTRACT

Objective: In this study, the effects of gliclazides, a second generation sulfonylurea group, on BDNF and NGF plasma levels, which are considered neurodegeneration biomarkers, will be examined. When designing our study, we assumed that gliazides might have positive neuronal effects. Thus, the possible positive effects of gliclazide will be emphasized in our study.

Methods: In the experiment, 21 adult male Wistar-Albino rats were used. Serum BDNF and NGF levels were determined by analyzing with enzyme-linked immunosorbent assay kit in accordance with the recommendations.

Results: BDNF levels were significantly lower in gliclazide-treated diabetic rats and non-medicated diabetic rats compared to the healthy control group (p=0.017, p<0.001, respectively). Although the BDNF level of rats with diabetes given gliclazide was increased compared to rats with and without diabetes, this difference was not significant (p=0.107). Similarly, NGF levels were significantly lower in rats given gliclazide (p=0.009) and diabetic rats not given gliclazide (p=0.001) compared to the healthy control group. When the diabetic groups were compared among themselves, although the NGF level was increased in the gliclazide group, this difference was not statistically significant (p=0.638). The differences between the groups were significant in cyclic AMP regulatory element binding (p<0.001), c-FOS (p<0.001), amyloid precursor protein (p<0.001), B-SECRETASE1 (p=0.004), and doublecortin (p<0.001) levels.

Conclusion: As a result, serum BDNF and NGF levels were significantly higher in non-diabetic healthy control group rats than in diabetic rats. While low serum levels of BDNF and NGF neurotrophins, which increase in neurodegeneration, were observed in diabetic rats, this level was observed to be higher in diabetic rats given gliclazide.

INTRODUCTION

Glucose metabolism is essential for normal brain function, and circulating glucose levels play an important role in learning and memory functions. Neurotrophins are important regulators in the development and functioning of the nervous system. Neurotrophin family members are nerve growth factor (NGF), brain-derived neurotrophic factor, neurotrophin-3, neurotrophin-4/5, neurotrophin-6, and neurotrophin-7.[1,2]

Brain-derived neurotrophic factor (BDNF) is an important neurotrophin that affects the survival, growth, and function of neurons in the central nervous system (CNS) and peripheral nervous system (PNS); stabilizes synapses; and regulates synaptic function, axon, and dendrite branching. While BDNF mainly helps neurons to develop and renew themselves in the CNS, it contributes to the structural health and maintenance of important nerve pathways in which neurotransmitters function.[3] NGF is an important neuropeptide of the neurotrophin family, as a complex composed of three non-covalently linked subunits. Other proteins such as cyclic AMP Regulatory Element Binding Protein (CREB) and cFOS are also a transcription factor involved in the development, maintenance, and neuronal plasticity of the nervous system, as well as learning and memory.[4]

Studies have shown that the deficiency in the synthesis of BDNF, which plays a critical role in the long-term potential based on learning and memory, may increase the susceptibility to neurological and neurodegenerative diseases such as type 2 diabetes mellitus (T2DM), Huntington's disease, and Alzheimer's disease in humans and animals.[3,5] NGF is a neurotrophic protein that has been shown to increase the growth, differentiation, and survival of nerve cells in mammals.[6]

Sulfonylureas act by increasing insulin secretion in pancreatic beta cells and are drugs used in the treatment of T2DM for more than 50 years. Its main effects are to re-

duce fasting hyperglycemia. Sulfonylureas are divided into two groups: First and second-generation sulfonylureas. Second-generation sulfonylureas (glyburide, glipizide, glimepiride, and gliclazide) are more potent and possibly safer than first-generation sulfonylureas. They are usually metabolized by the liver. Second-generation sulfonylureas are excreted both in the urine and in the feces. Second-generation sulfonylureas are non-ionically bound to plasma proteins and are more potent, and drug interactions are minimal.[7]

Neurotrophins are synthesized from many cell types in the CNS, PNS, and peripheral tissues and are known to have biological effects both in the nervous system and in many tissues outside the nervous system. It is accepted that the deficiency in neurotrophin synthesis is related to the increased susceptibility to neurodegenerative diseases.

In this study, the effects of gliclazides, a second generation sulfonylurea group, on BDNF and NGF plasma levels, which are considered neurodegeneration biomarkers, will be examined. When designing our study, we assumed that gliazides might have positive neuronal effects. Thus, the possible positive effects of gliclazide will be emphasized in our study.

MATERIALS AND METHODS

This study was carried out at Dicle University Health Sciences Application and Research Center. Ethical approval for the study was obtained from Dicle University Animal Experiments Local Ethics Committee (Date: April 17, 2023, Acceptance Number: 482040). Procedures were performed in accordance with standard experimental animal studies ethics.

Animals and Creation of Diabetes

In the experiment, 21 adult male Wistar-Albino rats, 8–10 weeks old, with an average weight of 250–300 g, obtained from Dicle University Health Sciences Application and Research Center, were used. Rats were fed in stainless steel cages at 22±2°C for 8 weeks with normal diet and tap water for 12 h in light and 12 h in darkness without any restriction.

A single dose of nicotinamide (110 mg/kg) was administered to the abdominal cavity of rats to induce experimental diabetes. Fifteen minutes after nicotinamide administration, streptozotocin (STZ), which was prepared by dissolving 14 rats allocated for diabetic groups in 0.1 M citrate buffer (Ph 4.5), was administered to each rat intraperitoneally as a single dose of 60 mg/kg (Sigma-Aldrich, Co., St. Louis, MO, USA). To prevent hypoglycemia, a possible side effect of STZ, 5% glucose was added to the drinking water of the rats in the first 48 h after the injection. Animals with a blood glucose level above 250 mg/dL measured by glucometer from the tail vein after 72 h following the injection were considered as diabetic.

Twenty-one Wistar Albino rats were divided into 3 groups of 7 each. Group 1 (n=7): Control group without diabetes. These rats were given only placebo (tap water) in addition to the normal diet for 8 weeks. Group 2 (n=7): Control group with diabetes. Diabetes was induced in these rats and only placebo (tap water) was given for 8 weeks in addition to the normal diet. Group 3 (n=7): Diabetes was established and treated with gliclazide (10 mg/kg/day) for 8 weeks in addition to normal diet and tap water.

At the end of the 8-week experiment, blood was drawn from the heart of the rats by exsanguination under mild ketamine anesthesia and the rats were sacrificed. Glucose levels of blood samples were measured with Abbott Diagnostics original kits and Abbott Architect C1 Photometric Autoanalyzer (Abbott Laboratories, Abbott Park, IL, USA). In addition, serum BDNF, NGF, TDP-43, amyloid precursor protein (APP), β-secretase 1, CREB, and c-FOS levels from blood samples were determined by analyzing in accordance with the recommendations of the enzyme-linked immunosorbent assay kit (Sunred Biological Technology, Shanghai, China) manufacturer. Results were read at 450 nm and expressed in pg/mL and ng/mL.

Statistical Analysis

Statistical analysis was performed using the SPSS 26.0 (SPSS Inc., Chicago, IL, USA) program. Shapiro–Wilk test was used for normal distribution evaluation. Arithmetic mean ± standard deviation will be used for continuous variables with a normal distribution, and frequency and percentage will be used for categorical variables. Analysis of variance (ANOVA) test was used for comparisons of our continuous data and Tukey's test was used for in-group comparisons. Chi-square test will be used for categorical variables. The relationship between the two numerical variables was examined by Spearman correlation analysis and the $p<0.05$ value was considered significant for all evaluations.

RESULTS

The ANOVA test aggregated result of BDNF, NGF, and other neurodegeneration markers are shown in Table 1. BDNF was 0.22±0.03 ng/mL in healthy rats, 0.13±0.02 in non-medicated diabetic rats, and 0.16±0.04 ng/mL in glycoside-treated diabetic rats (Fig. 1). The difference between the groups was significant ($p<0.001$). NGF levels were 4.39±1.13, 2.76±0.20, and 3.11±0.44 ng/mL in healthy rats, non-medicated diabetic rats, and glycoside-treated diabetic rats, respectively (Fig. 2). The difference was statistically significant ($p=0.001$). In the ANAVO test analysis, the differences between the groups were significant in CREB ($p<0.001$), c-FOS ($p<0.001$), APP ($p<0.001$), B-SECRETASE1 ($p=0.004$), and doublecortin (DCX) ($p<0.001$) levels. However, TDP-43 level was similar in all three groups and the difference was not significant ($p=0.166$).

Intra-group comparisons of BDNF and NGF levels are

Table 1. Distribution of BDNF. NGF and other neurodegeneration markers in rats

Variables	Group 1	Group 2	Group 3	P for ANOVA test
Glucose (mg/dL)	100.29± 9.34	541.29±21.27	421.29±10.62	<0.001
BDNF (ng/mL)	0.22±0.03	0.13±0.02	0.16±0.04	<0.001
NGF (ng/mL)	4.39±1.13	2.76±0.20	3.11±0.44	0.001
CREB (ng/L)	375.43±36.22	218.29±25.80	253.57±13.11	<0.001
c-FOS (ng/mL)	4.53±0.75	2.56±0.31	3.16±0.15	<0.001
APP (ng/mL)	1.09±0.24	2.12± 0.14	1.12±0.17	<0.001
B-SECRETASE1 (ng/mL)	2.52±0.45	3.44±0.44	2.76±0.47	0.004
TDP-43 (pg/mL)	293.00±22.96	312.00±7.50	308.86±22.63	0.166
DCX (ng/mL)	52.12±3.82	39.28±2.94	40.95±6.47	<0.001

APP: Amyloid precursor protein; BDNF: Brain-derived neurotrophic factor; CREB: Cyclic AMP response element binding protein; DCX: Doublecortin; NGF: Nerve growth factor; TDP-43: TAR DNA binding protein 43 (p<0.05 or p<0.01).

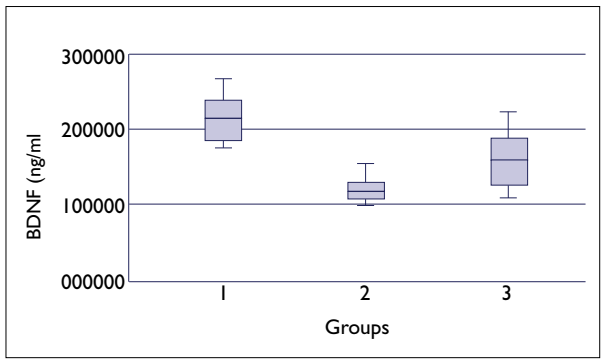

Figure 1. Brain-derived neurotrophic factor level in diabetic induced rats and healthy controls.

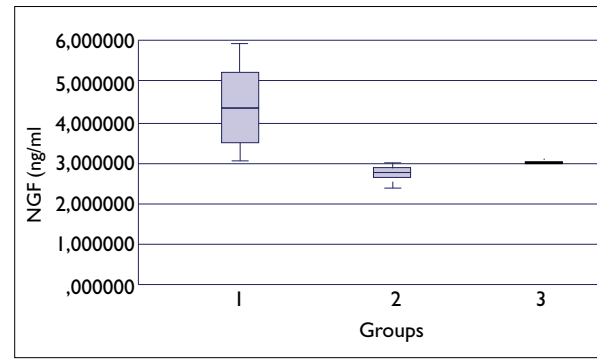

Figure 2. Nerve growth factor level in diabetic induced rats and healthy controls.

Table 2. Intragroup comparison of neurodegeneration biomarkers BDNF and NGF in rats

Parameters	Groups				
	1	2	3	Groups comparison	Tukey test P*
BDNF (ng/mL)	0.22±0.03	0.13±0.02		1&2	<0.001
	0.22±0.03		0.16±0.04	1&3	0.017
		0.13±0.02	0.16±0.04	2&3	0.107
NGF (ng/mL)	4.39±1.13	2.76±0.20		1&2	0.001
	4.39±1.13		3.11±0.44	1&3	0.009
		2.76±0.20	3.11±0.44	2&3	0.638

BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor (p<0.05 or p<0.01).

shown in Table 2. The BDNF level was significantly lower in diabetic rats both given and not given gliclazide than the healthy control group (p=0.017, p<0.001, respectively). Although there was an increase in the BDNF level of rats with diabetes and those given gliclazide, this difference was not significant (p=0.107). Similarly, NGF levels were significantly lower in rats given gliclazide (p=0.009) and diabetic rats not given gliclazide (p=0.001) compared to the healthy control group. When the diabetic groups were compared among themselves, although the NGF level was increased in the gliclazide group, this difference was not statistically significant (p=0.638).

While BDNF has a positive correlation with CREB (R=0.642, p=0.002), c-FOS (R=0.740, p<0.001), and DCX (R=0.504, p=0.020), there was a negative correlation with

Table 3. Correlation of BDNF and NGF with other neurodegeneration biomarkers.

Parameters	BDNF (ng/ml) R.P	NGF (ng/ml) R.P
CREB (ng/L)	0.642, 0.002	0.74, <0. 000
c-FOS (ng/mL)	0.740, <0.001	0.653, 0.001
APP (ng/mL)	-0.552, 0.009	-0.474, 0.030
B-SECRETASE1 (ng/mL)	-0.419, 0.058	-0.483, 0.027
TDP-43 (pg/mL)	-0.171, 0.459	-0.380, 0.089
DCX (ng/mL)	0.504, 0.020	0.580, 0.580

APP: Amyloid precursor protein; BDNF: Brain-derived neurotrophic factor; CREB: Cyclic AMP response element binding protein; DCX: Doublecortin; NGF: Nerve growth factor; TDP-43: TAR DNA binding protein 43 ($p<0.05$ or $p<0.01$).

APP (R=−50.552, p=0.009), B-SECRETASE-1 (R=−0.419, p=0.058), and TDP-43 (R=−0.171, p=0.459) (Table 3). Similarly, while NGF was positively associated with CREB (R=0.74, p<0.001), c-FOS (R=0.653, p=0.001), and DCX (R=0.580, p=0.006), there was a negative correlation with APP (R=−0.474, p=0.030), B-SECRETASE-1 (R=−0.483, p=0.027), and TDP-43 (R=−0.380, p=0.089).

DISCUSSION

Our study showed that the levels of neurotrophins BDNF and NGF were significantly lower in diabetic rats given and not given gliclazide compared to the healthy control group. Although there was an increase in both BDNF and NGF levels in diabetic rats given gliclazide, this difference was not significant.

In diabetes, changes occur in the cerebral vessels and cause a decrease in blood fluidity. Subsequently, hypoxia and neuronal damage occur, respectively. This is because it results in lipid accumulation in brain vessels and ultimately various cerebrovascular endothelial dysfunctions.[8] Neurotrophins are responsible for increasing the survival and damage resistance of neurons. While the majority of neurotrophins are produced by the CNS, some are also produced by peripheral tissues. It is largely found in the hypothalamus, the limbic system, and other parts of the brain such as the hippocampal nucleus.[9] Central effects on brain tissue and effects on energy homeostasis are among the effects of BDNF. Studies have reported that BDNF is related to metabolic effects, especially glucose metabolism and insulin resistance. NGF is a neurotrophin that plays an important role in the normal development of the nervous system, the survival of nerve cells, and their function. It has been suggested that NGF plays an important role in the diagnosis and treatment of important diseases such as neurodegenerative diseases, cancer, pain, retinal diseases, or diabetes as well as other diseases.[9,10]

The most prescribed drugs in T2DM patients are sulfonylureas. They are highly preferred drugs with a decrease in the mean glycosylated hemoglobin rate, good safety profile, and positive effects on gastrointestinal tolerability.[11] Regardless, these antidiabetics have some undesirable effects. In addition to the antidiabetic effects of sulfonylureas, there may also be beneficial effects to be explored further. Gliclazide, a second-generation sulfonylurea group, has been reported to have a reducing effect on free radicals as well as regulating blood sugar.[11] Reduction of free radicals in circulation may result in amelioration of oxidative stress and perhaps prevention or delay of complications. In a study, it was reported that gliclazides have protective effects from cardiovascular system diseases by having a positive effect on plasma lipid profile and platelet functions.[12] Alp et al.[13] suggested that gliclazide is a substance that protects the brain and nerve tissues against diabetic oxidative stress.

Studies investigating the relationship between BDNF levels and glycemic parameters have shown conflicting results. While some studies have reported an increase in BDNF levels in T2DM patients, others have reported a decrease.[14,15] Increased BDNF levels have been reported in patients with T2DM receiving metformin therapy. In our study, gliclazide was given to diabetic mice, and we observed that the gliclazide level was higher in these mice than in diabetic mice that were not given gliclazide.

Studies have shown that NGF levels decrease significantly in cognitive disorders, exogenous NGF applications provide improvement in cognitive disorders, and NGF levels are significantly lower in diabetic patients.[16-18] The neurotropic and metabotropic potentials of NGF are thought to have an impact on the molecular mechanism and pathogenesis of diabetes, and multidisciplinary studies are being conducted on the NGF-DM interaction.[19] Boyuk et al.[20] reported that BDNF levels were higher in diabetic patients than in the healthy control group.

In our study, BDNF level and, similarly, NGF level were lower in diabetic rats compared to healthy rats. There was an increase in BDNF and NGF levels in rats with diabetes and given gliclazide. Moreover, in our study, BDNF showed positive correlation with NGF, CREB, and c-FOS neurodegeneration biomarkers, while there was negative correlation with APP, TDP-43, and DCX.

Our study has many limiting points. One of these limitations is the lack of histopathological examination of the nervous system. Since it is a rat model study, it has a limited number of samples.

Conclusion

As a result, serum BDNF and NGF levels were significantly higher in non-diabetic healthy control group rats than in diabetic rats. While low serum levels of BDNF and NGF neurotrophins, which increase in neurodegeneration, were observed in diabetic rats, this level was observed to be higher in diabetic rats given gliclazide. Although there are many studies on the effects of treatments on the nervous system as well as diabetic complexity, there is still not enough information on this subject. Detailed studies are needed to better understand the positive and negative effects of gliclazides, which are sulfonylurea antidiabetic drugs. We hope that our study will contribute to this issue.

Ethics Committee Approval

This study approved by the Dicle University, Faculty of Medicine Clinical Research Ethics Committee (Date: 17.04.2023, Decision No: E-35582840-020-482040).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: G.Ş.G., M.B.; Design: G.Ş.G.; Supervision: M.B.; Materials: G.Ş.G.; Data: G.Ş.G.; Analysis: M.B.; Literature search: G.Ş.G., M.B.; Writing: G.Ş.G., M.B.; Critical revision: M.B.

Conflict of Interest

None declared.

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Diabetes Mellituslu Sıçanlarda Gliklazid Kullanımının BDNF ve NGF Düzeylerine Etkisi

Amaç: Bu çalışmada, ikinci kuşak bir sülfonilüre grubu olan gliklazidlerin nörodejenerasyon biyobelirteçleri olarak kabul edilen BDNF ve NGF plazma düzeyleri üzerindeki etkileri incelenecektir. Çalışmamızı tasarlarken, gliazidlerin olumlu nöronal etkileri olabileceğini varsaydık. Gliklazidin olası olumlu etkileri çalışmamızda değerlendirildi.

Gereç ve Yöntem: Çalışmada 21 adet erişkin erkek Wistar-Albino sıçan kullanıldı. Öneriler doğrultusunda ELISA kiti ile analiz edilerek serum BDNF ve NGF düzeyleri belirlendi.

Bulgular: Glikazid verilen diabetik sıçanlarda ve ilaç verilmeyen diyabetik sıçanlarda BDNF düzeyi sağlıklı kontrol grubuna göre anlamlı olarak düşüktü (sırasıyla, p=0.017, p<0.001). Gliklazid verilen diyabetli sıçanların BDNF düzeyi, diabetli ve ilaç verilmeyen ratlara göre artış olmasına rağmen bu fark anlamlı değildi (p=0.107). Benzer şekilde, gliklazid verilen sıçanlarda (p=0.009) ve gliklazid verilmeyen diyabetik sıçanlarda (p=0.001) NGF seviyeleri sağlıklı kontrol grubuna göre anlamlı derecede düşüktü. Diyabetik gruplar kendi aralarında karşılaştırıldığında gliyazid grubunda NGF düzeyi artmış olmakla birlikte bu fark istatistiksel olarak anlamlı değildi (p=0.638). CREB (p<0.001), c-FOS (p<0.001) ve DCX (p<0.001) düzeyleri diyabetik sıçanlarda daha düşük idi.

Sonuç: Sonuç olarak, diyabetik olmayan sağlıklı kontrol grubu sıçanlarda serum BDNF ve NGF düzeyleri diyabetik sıçanlara göre anlamlı olarak yüksekti. Nörodejenerasyonda artan BDNF ve NGF nörotrofinlerinin serum düzeyleri diyabetik sıçanlarda düşük görülürken gliklazid verilen diyabetik sıçanlarda bu düzeyin daha yüksek olduğu gözlendi.

Anahtar Sözcükler: Beyin kaynaklı nörotrofik faktör (BDNF); gliklazid; nörodejenerasyon; sinir büyüme faktörü (NGF).

SCIE DOI: 10.14744/scie.2023.70493
South. Clin. Ist. Euras. 2023;34(4):312-319

Original Article

Evaluation of the Clinical Characteristics of the Patients Admitted to the Emergency Department with the Symptoms or Suspicion of COVID-19

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Submitted: 05.09.2022
Revised: 07.08.2023
Accepted: 08.08.2023

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Keywords: Clinical symptoms; coronavirus disease; COVID-19; emergency department; pandemic.

ABSTRACT

Objective: Emergency departments have been the first step in managing the COVID-19 infection, which has been declared a worldwide pandemic. This study aims to determine the clinical characteristics of patients admitted to the emergency department with the suspicion or symptoms of COVID-19 infection.

Methods: The sample of our study consisted of patients aged 18 and over who were admitted to the emergency department of a tertiary hospital in Istanbul with symptoms or suspicion of COVID-19 between September and December 2020. Five hundred patients with positive RT-PCR test results and 500 patients with negative test results were included in the study. The patients' data were retrieved retrospectively through the hospital's information management system.

Results: The mean age of patients with COVID -19 (-) (53.2±18.1) was lower than that of patients with COVID -19 (+) (59.2±18.4) (p=0.001). The distribution of sex (p=0.61) and occupation (p=0.52) was similar in both groups. The rate of presentation with dyspnea was higher in COVID -19 (+) patients (37.6%) than in the COVID -19 (-) group (22%) (p=0.001). Body temperature measured in the emergency department was higher in COVID -19 (+) patients than in COVID -19 (-) patients (p=0.04). Mean SPO2 was lower in COVID -19 (+) patients (92.3±9.6%) than in COVID -19 (-) patients (96.2±4.8%) (p=0.001). The incidence of ground-glass opacities in the thorax CT was higher (59.6%) in the COVID -19 (+) patient group than in the COVID -19 (-) (47.5%) patient group (p=0.003).

Conclusion: In this study, the clinical features of COVID-19 infection in patients admitted to the emergency department were compared with the literature. Conducting similar studies on COVID-19 infection is essential to update the existing literature and add new data. More comprehensive studies and evidence are needed to effectively manage the diagnosis and treatment process of the epidemic.

INTRODUCTION

In late 2019, a group of patients with pneumonia was reported in the city of Wuhan in China's Hubei province and is believed to be associated with a market selling seafood and fresh meat.[1] This newly discovered virus has been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) and the disease has been named coronavirus disease 2019" (COVID-19).[2] The World Health Organization declared COVID-19 a pandemic on March 11, 2020.[3]

The most common symptoms in the clinical course of COVID-19 are fever, cough, fatigue, and gastrointestinal symptoms. Factors that increase the severity of the disease include comorbid illnesses and significant laboratory abnormalities.[4] Although COVID-19 has almost the same symptoms as other coronaviruses, it can cause severe interstitial pneumonia, acute respiratory distress syndrome, and subsequently multiorgan failure in elderly patients or in some high-risk individuals with two or more comorbid diseases.[5] Current evidence shows that the main risk factors for poor outcomes are advanced age, a history of ischemic heart disease, hypertension (HT), diabetes mellitus (DM), and chronic lung disease.[6] Further examination and

treatment revealed bilateral pulmonary infiltrates on computed tomography of the chest (CT) and white blood cell (WBC) depletion on laboratory results.[7] Reverse transcriptase polymerase chain reaction testing (RT-PCR) with nasopharyngeal swab specimens from the upper airways and sputum, broncho-alveolar lavage, and tracheal aspirate specimens from the lower airways is required to confirm the diagnosis.[8]

The aim of this study is to describe and investigate the clinical characteristics of patients presenting to the emergency department with symptoms or suspected COVID-19. Although the mortality rate and the number of hospitalizations due to the COVID-19 infection have decreased, many patients are still admitted to the hospital. Given the nationwide and worldwide spread of the epidemic and the risk of new variants manifesting in the coming years, knowledge of the infection is essential for controlling the epidemic and protecting individuals. With the results of this study, patients admitted to the emergency department with a prediagnosis of COVID-19 should be accurately identified, and rapid and effective triage should be performed. Our study, in which we retrospectively investigated the signs and symptoms of COVID-19 infection and the clinical course of patients, is intended to contribute to the literature.

MATERIALS AND METHODS

This retrospective, descriptive study was conducted in the emergency department of a tertiary hospital in Istanbul. Kartal Dr. Lutfi Kirdar City Hospital where the study was conducted is one of the largest tertiary hospitals on the Anatolian side of Istanbul. During the pandemic, like several pandemic hospitals in Istanbul, it served a large population and had accepted approximately 200,000 patient applications by December 2020. The study sample consisted of patients over 18 years of age admitted to the hospital emergency department between September and December 2020 with symptoms or suspected COVID-19 according to ICD 10 (international statistical classification of diseases and related health problems) (patients with ICD code Z03.8 Observation for other suspected diseases and conditions and ICD code U03.7 COVID-19, identified virus). The period from September to December 2020, when the study was conducted, is the period of the second wave of the pandemic in Turkiye, when an increase in patient admissions to the emergency department was observed.

To compare clinical parameters, data from 500 COVID-19 (+) and 500 COVID-19 (−) patients was examined. The Openepi application was used to calculate the sample size of the study. Considering information from the literature, the required sample size was calculated to be 434 with a 95% confidence interval and 80% power based on the prevalence of COVID-19 symptoms at emergency department visits (if the prevalence of diarrhea is 3.5%, the prevalence of diarrhea in COVID-19 positive individuals is 10%).

Patient data were retrieved retrospectively through the hospital's information management system and recorded in the data collection instrument created by the researchers. Sociodemographic characteristics, reason for admission, current clinical signs and symptoms, risk factors, contact and travel history, vital signs measured in the emergency department, laboratory test and radiological imaging results (CT), clinical course, treatment methods used, and discharge status were recorded in the data collection form. In analyzing patient data, the total number of hospital admissions was evaluated, and data on COVID-19 symptoms and suspicions on initial admission were included in the study.

Statistical Analyses

Statistical analyses were performed using the statistical package for the social sciences 21.0 program. Descriptive characteristics were expressed as mean, standard deviation, and percentage. The fit of the data to the normal distribution was analyzed using the Kolmogorov-Smirnov test. Chi-square analysis was used to compare the distributions between groups, and the Student's t-test was used to compare the means because the parametric conditions were met. The significance level was set at a $p<0.05$.

RESULTS

Our aim in this study was to compare the clinical characteristics of coronavirus disease with the literature by examining them in negative and positive patient groups. The sociodemographic characteristics of the patients are shown in Table 1. Among the patients participating in the study, the mean age of patients with COVID-19 (−) was lower than that of patients with COVID-19 (+) (53.2±18.1 vs. 59.2±18.4; p=0.001) (Table 1).

The patients' complaints, vital signs, radiological findings, and RT-PCR test results on admission to the emergency department are shown in Table 2. Among the patients who participated in the study, the rate of admission with fever was higher in the COVID-19 (−) patients (22.8%) than in patients with COVID-19 (+) (16.6%) (p=0.01). The rate of patients with dyspnea (22%) was lower in the COVID-19 (−) patient group than in the COVID-19 (+) patient group (37.6%) (p=0.001). The mean oxygen saturation (SpO_2) of COVID-19 (+) patients (92.3±9.6%) was lower than that of COVID-19 (−) (96.2±4.8) patients (p=0.001). The time between symptom onset and the RT-PCR test was 3.9 days in COVID-19 (+) patients and 3.3 days in COVID-19 (−) patients (p=0.001). In the imaging results of the patients, ground glass opacities were seen more frequently in COVID-19 (+) patients (59.6%) than in COVID-19 (−) (47.5%) patients (p=0.003) (Table 2).

The risk factors and chronic diseases of the patients are shown in Table 3. The rate of advanced age was higher (41%) in patients with COVID-19 (+) than in patients with COVID-19 (−) (29.2%) (p=0.001). The frequency of chronic diseases was higher in COVID-19 (+) patients

Table 1. Sociodemographic characteristics of the patients

	Total	COVID-19 (-)	COVID-19 (+)		
	n (%)	n (%)	n (%)	t / χ^2	p
Age (X±SD)	56.22±18.49	53.2±18.1	59.2±18.4	-5.18	0.001
Gender					
Male	530 (53.0)	265 (53.0)	265 (53.0)	0.00	0.61
Female	470 (47.0)	235 (47.0)	235 (47.0)		
Occupation					
Healthcare worker	53 (5.3)	25 (5.0)	28 (5.6)	0.179	0.52
Other	947 (94.7)	475 (95.0)	472 (94.4)		
History of contact in the last 14 days					
No	768 (76.8)	378 (75.6)	390 (78.0)	1.82	0.37
Yes	232 (23.2)	122 (24.4)	110 (22.0)		

Student t-test; Chi-square test. X: Mean; SD: Standard deviation.

(54.8%) than in COVID-19 (−) patients (34.6%) (p=0.001). When assessing patients' comorbidities, it was found that the incidence of DM was higher in the group of COVID-19 (+) patients (22%) than in the group of COVID-19 (−) patients (11.6%) (p=0.001) (Table 3).

The clinical course of patients admitted to the hospital is shown in Table 4. While 5.8% of COVID-19 (+) patients were transferred from the emergency department to the intensive care unit, this rate was 1.8% in the COVID-19 (−) group. When assessing patients' need for ventilatory

Table 2. Complaints, vital signs, radiological and RT-PCR test results of patients on admission to the emergency department

	Total	COVID-19 (-)	COVID-19 (+)		
Complaints on admission	n (%)	n (%)	n (%)	χ^2	p
Fever	197 (19.7)	114 (22.8)	83 (16.6)	6.08	0.01
Cough	262 (26.2)	120 (24.0)	142 (28.5)	2.56	0.11
Shortness of breathing	298 (29.8)	110 (22.0)	188 (37.6)	29.08	0.001
Loss of taste and smell	28 (2.8)	12 (2.4)	16 (3.2)	0.59	0.44
Headache	76 (7.6)	47 (9.4)	29 (5.8)	4.61	0.03
Fatigue	225 (22.5)	114 (22.8)	111(22.2)	0.04	0.83
Muscle pain	128 (12.8)	74 (14.8)	54 (10.8)	3.58	0.06
Sore throat	84 (8.4)	67 (13.4)	17 (3.4)	32.49	0.001
Nausea - vomiting	92 (9.2)	40 (8.0)	52 (10.4)	1.72	0.19
Diarrhea	60 (60.0)	33 (6.6)	27 (5.4)	0.65	0.42
Other complaints	225 (22.5)	85 (17.0)	140 (28.0)	17.21	0.001
Findings on admission	**n (%)**	**n (%)**	**n (%)**	**t / χ^2**	**p**
Fever (oC) (X±SD)	36.9±0.7	36.6±0.7	37.2±0.6	-0.86	0.04
SpO_2 (X±SD)	94.4±7.8	96.2±4.8	92.3±9.6	7.37	0.001
RT-PCR in the ED					
Not tested	266 (26.6)	17 (3.4)	249 (49.8)	276.61	0.001
Tested	734 (73.4)	483 (96.6)	251 (50.2)		
Time from symptom onset to RT-PCR test (days) (X±SD)	2.7±3.8	1.5±3.3	3.9±3.9	12.46	0.001
Ground glass opacities in thorax CT					
No	278 (45.1)	126 (52.5)	152 (40.4)	8.63	0.003
Yes	338 (54.9)	114 (47.5)	224 (59.6)		

Student t-test; Chi-square test; X: Mean; SD: Standard deviation; RT-PCR: Reverse transcriptase polymerase chain reaction; SpO_2: Oxygen saturation; ED: Emergency department; CT: Computed tomography.

Table 3. Patients' chronic diseases and risk factors for COVID-19

	Total	COVID-19 (-)	COVID-19 (+)		
	n (%)	n (%)	n (%)	χ^2	p
Advanced age	351 (35.1)	146 (29.2)	205 (41.0)	15.28	0.001
Smoking	23 (2.3)	11 (2.2)	12 (2.4)	0.46	0.83
Any chronic disease	447 (44.7)	173 (34.6)	274 (54.8)	17.19	0.001
Diabetes mellitus	168 (16.8)	58 (11.6)	110 (22.0)	19.35	0.001
Hypertension	223 (22.3)	78 (15.6)	145 (29.0)	25.91	0.001
Chronic respiratory disease	90 (9.0)	40 (8.0)	50 (10.0)	1.22	0.27
Cardiovascular disease	114 (11.4)	39 (7.8)	75 (15.0)	12.83	0.001
Cerebrovascular disease	29 (2.9)	12 (2.4)	17 (3.4)	0.89	0.35
Chronic kidney failure	43 (4.3)	15 (3.0)	28 (5.6)	4.11	0.04
Cancer	48 (4.8)	24 (4.8)	24 (4.8)	0	0.99
Other	48 (4.8)	12 (2.4)	36 (7.2)	12.61	0.001

Chi-square test.

Table 4. Clinical course of the patients in hospital

	Total	COVID-19 (-)	COVID-19 (+)		
	n (%)	n (%)	n (%)	χ^2	p
Discharge against medical advice					
Yes	16 (1.6)	5 (1.0)	11 (2.2)	2.29	0.13
No	983 (98.4)	495 (99.0)	488 (97.8)		
Post-ED course					
Death	5 (0.5)	1 (0.2)	4 (0.8)	466.11	0.001
Transfer to ICU	38 (3.8)	9 (1.8)	29 (5.8)		
Transfer to ward	288 (28.8)	88 (17.6)	200 (40.0)		
Treated at home	235 (23.5)	24 (4.8)	211 (42.2)		
Observed at home	411 (41.1)	369 (73.8)	42 (8.4)		
Treatment rejection	9 (0.9)	4 (0.8)	5 (1.0)		
Transfer to another institution	14 (1.4)	5 (1.0)	9 (1.8)		
Need for respiratory support during hospitalization					
No	67 (20.6)	26 (26.8)	41 (18.0)	3.23	0.07
Yes	258 (79.4)	71 (73.2)	187 (82.0)		
Applied respiratory support					
Nasal oxygen support	64 (24.9)	21 (29.6)	43 (23.1)	-	0.09
Oxygen support with mask	110 (42.8)	33 (46.5)	77 (41.4)		
Non-invasive mechanical ventilation	1 (0.4)	1 (1.4)	0		
Invasive mechanical ventilation	82 (31.9)	16 (22.5)	66 (35.5)		

Chi-square test. ED: Emergency department; ICU: Intensive care unit.

support during hospitalization, the need for invasive mechanical ventilation was higher in the COVID-19 (+) patient group (35.5%) than in the COVID-19 (−) patient group (22.5%) (p=0.09) (Table 4).

The blood test results of patients in the emergency department are shown in Table 5. The mean WBC value of the COVID-19 (−) group of patients (9.7±4.8)(×103) was higher than the results of the COVID-19 (+) group (7.9±9.2) (×103) (p=0.004). The mean C-reactive protein (CRP) levels of COVID-19 (+) patients (72.4±72.9) were higher than the results of the COVID-19 (−) group (64.5±74.6) (p=0.20) (Table 5).

Table 5. Blood test results of the patients in the emergency department (n=266)

	Total	COVID-19 (-)	COVID-19 (+)		
	X±SD	X±SD	X±SD	t	p
WBC (10^3/uL)	8.6±7.9	9.7±4.8	7.9±9.2	2.88	0.004
HGB (gr/dl)	12.8±3.7	12.6±2.2	12.9±4.3	-1.10	0.27
PLT (10^3/uL)	236.9±107.1	250.0±114.8	229.1±101.6	2.49	0.01
LY (%)	19.4±12.6	18.8±12.0	19.8±12.8	-0.98	0.33
NE (%)	71.8±14.6	72.7±13.9	71.3±14.9	1.15	0.25
Creatinine (mg/dl)	1.32±3.51	1.2±1.1	1.4±4.3	-0.80	0.42
AST (U/L)	39.6±34.9	33.2± 26.6	43.3±38.6	-3.67	0.001
ALT (U/L)	33.8±35.7	32.5±37.5	34.5±34.6	-0.69	0.49
CK (U/L)	189.8±318.8	115.1±150.4	237.3±382.5	-4.01	0.001
CRP (mg/L)	69.7±73.5	64.5±74.6	72.4± 72.9	-1.28	0.20
Troponine T	0.04±0.13	0.06± 0.19	0.03±0.07	1.67	0.09
D-Dimer	1162.1±1263.5	1166.3±1322.8	1160.3±1241.5	0.04	0.97

Student t-test. X: Mean; SD: Standard deviation. WBC: White Blood Cell; HGB: Hemoglobin; PLT: Plateletes; LY: Lymphocytes; NE: Neutrophils; AST: Aspartate aminotransferase; ALT: Alanine aminorasaminase; CK: Creatine kinase; CRP: C-reactive Protein.

DISCUSSION

Knowledge of the symptoms, risk factors, and clinical course of COVID-19 disease is important for its management. The results of our study show that in the COVID-19 (+) group, 37.6% of patients were admitted to the emergency department with dyspnea. When the patients' concomitant diseases were evaluated, it was found that in COVID-19 (+), 29% of the patients had HT. In the radiological imaging results, it was found that the percentage of ground glass areas in the thorax CT of the COVID-19 (+) patient group was 59.6%.

Looking at data from the beginning of the pandemic to the present, mortality rates are reported to be higher in males than in females.[9] In a systematic review and meta-analysis of 57 studies evaluating sex differences in the acquisition of COVID-19, the pooled prevalence of confirmed COVID-19 cases was 55.00 in males and 45.00 in females, suggesting that COVID-19 is more prevalent in males than in females.[10] In a study of 498 patients conducted by Tanyeri during the first wave of the pandemic, the mean age of patients with positive test results was 45±20 years, and 68% of cases were male, whereas the mean age of patients with negative test results was 56±22 years, and 64% of cases were male.[11] The reason why the male sex is more affected by the disease than the female sex can be explained by the fact that the male sex is more susceptible to infection compared with the female sex, which depends on factors such as hormonal status, immune function, and lifestyle.[9] In our study, we found that the mean age of patients with COVID-19 (+) was higher than that of patients with COVID-19 (−) (59.2±18.4 vs. 53.2±18.1; p=0.001), the sex distribution was similar (p=0.61), and the percentage of female patients was 47%. Based on these data, we can say that there is no association between sex and the acquisition of COVID-19 in our study.

In our study, 5.6% of individuals admitted to the emergency department with symptoms or suspected COVID-19 were health professionals. Determining the prevalence of SARS-CoV-2 infection among health care workers worldwide is critical to controlling the pandemic. The study by Gómez-Ochoa et al.[12] reported that nurses were the most commonly affected and that the prevalence of SARS-CoV-2 among health care workers was 11%.Compared with the general population, the rate of emergency department visits due to COVID-19 is reported to be three times higher,[13] and the test positivity rate is 11 times higher among health care workers working in hospitals.[14] It is undeniable that health care professionals, especially those working in emergency departments, are at risk during the pandemic period. Given all these data, it is of great importance that health care professionals who play an active role in patient care should be vigilant about the use of personal protective equipment.[14]

Thorax CT is a quick and easy method for the early diagnosis of COVID-19. In the systematic review and meta-analysis by Bao et al.,[15] the most common pathologies among the investigated thoracic findings were CT ground-glass opacities (83.31%) and mixed consolidated ground-glass opacities (58.42%).In a study examining the relationship between RT-PCR tests and CT thoracic findings in 167 patients, it was reported that patients with negative RT-PCR test results had areas compatible with COVID-19 in their CT thoracic findings.[16] In our study, the frequency of ground-glass opacities was 59.6% in COVID-19 (+) patients and 47.5% in COVID-19 (−) patients (p=0.003). Although the RT-PCR test results of many patients admitted to our emergency department with suspected COVID-19 were negative, the presence of ground-glass opacities in the thorax CT may be related to the low sensitivity of the test and a negative test result in the early stages of the disease.

Based on the results of a systematic review, the optimal time to perform RT-PCR testing is between the 1st and 7th days after symptom onset, with the highest positive result rate seen at a mean of 6.72 days.[17] In our study, the time between the onset of symptoms and the RT-PCR test was 2.7±3.8 days in all patients, while this period was 3.9 days in COVID-19 (+) patients and 3.3 days in COVID-19 (−) patients (p=0.001). The fact that in our patients the RT-PCR test was performed in the early phase of symptoms might have influenced the test results. The difference in the time of admission of patients to the emergency room could be due to the difference in the perception of the disease, as well as the difficulty in accessing the hospital due to the restrictions in place throughout the country and the fact that patients did not go to the hospital out of concern for COVID-19 infection in the hospital. Nevertheless, it can be said that patients visited the emergency room in a reasonable time. In other studies, the number of days between symptoms and admission to the emergency department (possibly RT-PCR tests) was reported to be about 3 days.[18]

Knowledge of the clinical features of diseases and their prognosis is particularly important for the prevention of infectious diseases.[19] Many studies have reported that fever, shortness of breath, cough, and fatigue are the most common symptoms seen at the onset of the disease.[19-21] In the study by Guan et al.,[22] the most common symptoms in COVID-19 (+) patients were fever (43.8%) and cough (67.8%).In our study, the rate of admission to the emergency department with fever was found to be higher in COVID-19 (−) patients (22.8%) than in COVID-19 (+) patients (16.6%) (p=0.01). The higher rate of fever on admission in our study in COVID-19 (−) patients might be due to the fact that patients thought their fever was related to COVID-19. The fact that fever is the top symptom of COVID-19 in social media and other mass media creates the perception that fever is the most common symptom of coronavirus disease in society. It can be said that this perception affects the number of emergency room admissions by associating fever in individuals with COVID-19, even when it is due to other illnesses.

In the study by Wei et al.,[23] it was reported that 30.1% of patients had leukopenia, 75% had lymphocytopenia, 31.5% had thrombocytopenia, and 60.9% had high CRP. In the study by Zhang et al.,[24] an increase in WBC (p<0.001), neutrophil count (p<0.001), aspartate aminotransaminase (AST) (p<0.001), alanine aminotransaminase (p=0.015), and CRP (p<0.001), and a decrease in lymphocyte count (p<0.001) were reported. In our study, the mean WBC value of the COVID-19 (+) group of patients was found to be lower compared to COVID-19 (−) patients (p=0.004). The CRP values of COVID-19 (+) patients were higher than those of COVID-19 (−) patients (p=0.20).

According to current data, patients with a history of chronic disease are in the risk group for infection with COVID-19 and a poor prognosis.[25] Yang et al.[26] reported that HT (21.1%) and diabetes (9.7%) were the most common comorbidities observed in patients infected with COVID-19. According to the results of a meta-analysis study examining the prevalence of underlying diseases in COVID-19 cases, the most common diseases were HT (16.37%), cardiovascular disease (12.11%), DM (7.87%), chronic renal failure (0.83%), malignant disease (0.92%), and chronic obstructive pulmonary disease (0.95%).[25] In our study, the incidence of HT in COVID-19 (+) patients was 29.0%, and the rate of DM was 22%. The fact that a history of chronic disease increases susceptibility to COVID-19 infection can be explained by the fact that the drugs used and disease symptoms affect cellular immunity. Existing chronic diseases form the basis for further diseases.

As with the SARS and Middle East respiratory syndrome epidemics, mortality has been reported to increase with age in the COVID-19 pandemic.[6] Susceptibility to infection has been reported to be increased in adults over 60 years of age compared with younger or middle-aged groups.[27] In our study, COVID-19 (+) patients were found to be older in age (>65 years) (41% vs. 29.2%) (p=0.001). It can be speculated that the reasons for susceptibility to COVID-19 infection in advanced age are inability to self-care and dependence, taking multiple medications, and insufficient immunity to infections due to additional diseases.

It has been reported that the mortality rate of patients infected with COVID-19 who are in the intensive care unit and require mechanical ventilation is high.[28] In the study by Ciceri et al.,[29] it was reported that 23.1% of 410 patients died, 5.9% were further hospitalized, and 71% were discharged. In a study of 1336 patients in Turkiye, it was reported that 88% of patients were transferred to the ward, 8.5% were treated as outpatients, 3.5% were transferred to the intensive care unit, and 4.5% of cases died.[30] In our study, 0.8% of COVID (+) cases died in the emergency department. While 42.2% of patients were treated at home, 8.4% were followed up at home. 5.8% of patients were transferred to the ICU (p=0.001). While 74% of the negative group required home follow-up without treatment, more than 90% of the positive group required treatment. In the study by Chang et al.,[28] the ICU admission rate was 21%, and it was reported that 69% of cases required invasive mechanical ventilation. In our study, the rate of invasive mechanical ventilation in COVID-19 (+) patients was 35.5%. The need for invasive mechanical ventilation arises in acute respiratory failure in COVID-19 (+) patients. Clinicians should provide mechanical ventilation support in the early period to ensure and maintain respiratory function. In mechanical ventilation applications, attention should be paid to the use of personal protective equipment, and necessary precautions should be taken to avoid contamination with aerosols.

There are some limitations to the study that should be mentioned. One limitation of our study is that it was conducted at a single center. Since it is known that this long-lasting pandemic has different characteristics in each wave,

the period of the study should also be considered when interpreting the results.

Conclusion

In our study, confirming the results of previous studies, the frequency of shortness of breath was higher than other symptoms in COVID-19 (+) patients. Risk factors for the condition in our study included advanced age and chronic disease. In our study, the most common chronic disease in COVID-19 (+) patients was HT, followed by DM. In our study, 0.8% of COVID-19 (+) patients died in the emergency department, and 5.8% of patients were transferred to the intensive care unit.

During epidemics, it is important for disease control and protection of individuals to keep emergency department staff knowledge of triage, diagnosis, and treatment up to date. Patients admitted to the emergency department with a diagnosis and suspicion of COVID-19 should be correctly identified, and their triage performed quickly and efficiently. It is anticipated that the results of this study will contribute to the literature on the diagnosis and triage of COVID-19 in emergency departments.

Ethics Committee Approval

This study approved by the Istanbul University - Cerrahpaşa Non-Interventional Clinical Research Ethics Committee (Date: 15.02.2021, Decision No: 2020/49).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Ş., Z.T.; Design: S.Ş., Z.T., E.Y.; Supervision: Z.T., E.Y.; Data collection: S.Ş.; Analysis: S.Ş., Z.T., E.Y., E.D.K.T.; Literature search: S.Ş., E.D.K.T.; Writing: S.Ş., E.D.K.T., Z.T., E.Y.; Critical revision: Z.T., E.Y.

Conflict of Interest

None declared.

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Acil Servise COVID-19 Semptomları veya Şüphesi ile Başvuran Hastaların Klinik Özelliklerinin Değerlendirilmesi

Amaç: Acil servisler, dünya çapında bir pandemi olarak ilan edilen COVID-19 enfeksiyonunun yönetiminde ilk adım olmuştur. Bu çalışma, COVID-19 enfeksiyonu şüphesi veya semptomları ile acil servise başvuran hastaların klinik özelliklerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Çalışmamızın örneklemini Eylül-Aralık 2020 tarihleri arasında İstanbul'da üçüncü basamak bir hastanenin acil servisine COVID-19 semptomu veya şüphesi ile başvuran 18 yaş ve üzeri hastalar oluşturmuştur. RT-PCR test sonucu pozitif olan 500 hasta ile negatif olan 500 hasta çalışmaya dahil edildi. Hastaların verileri hastanenin bilgi yönetim sistemi aracılığıyla retrospektif olarak değerlendirildi.

Bulgular: COVID-19 (-) hastaların yaş ortalaması (53.2±18.1) COVID-19 (+) (59.2±18.4) olanlara göre daha düşüktü (p=0.001). Cinsiyet (p=0.61) ve meslek (p=0.52) dağılımları her iki grupta benzerdi. COVID-19 (+) hastalarda nefes darlığı ile başvuru oranı (%37.6) COVID-19 (-) gruba (%22) göre daha yüksekti (p=0.001). Acil serviste ölçülen vücut sıcaklığı COVID-19 (+) hastalarda COVID-19 (-) hastalara göre daha yüksekti (p=0.04). SPO_2 ortalaması COVID-19 (+) hastalarda (%92.3±9.6) COVID-19 (-) hastalara (%96.2±4.8) (p=0.001) göre daha düşük bulundu. Toraks BT'de buzlu cam opasitesi insidansı COVID-19 (+) hasta grubunda (%59.6) COVID-19 (-) hastalara (%47.5) göre daha yüksek bulundu (p=0.003).

Sonuç: Bu çalışmada, acil servise başvuran hastalarda COVID-19 enfeksiyonunun klinik özellikleri literatür ile karşılaştırıldı. COVID-19 enfeksiyonu ile ilgili benzer çalışmaların yapılması mevcut literatürün güncellenmesi ve yeni verilerin eklenmesi açısından önemlidir. Salgının teşhis ve tedavi sürecini etkin bir şekilde yönetmek için daha kapsamlı çalışmalara ve kanıtlara ihtiyaç vardır.

Anahtar Sözcükler: Acil servis; COVID-19; Coronavirüs Hastalığı; klinik semptomlar; pandemi.

SCIE DOI: 10.14744/scie.2023.68725
South. Clin. Ist. Euras. 2023;34(4):320-325

Original Article

Assessment of "Online Therapy" and "Telepsychiatry" Topics in the COVID-19 Pandemic Based on Google Trends Data

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Submitted: 04.07.2022
Revised: 06.03.2023
Accepted: 08.03.2023

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Keywords: Google trends; infodemiology; online therapy; telepsychiatry.

ABSTRACT

Objective: With the announcement of the pandemic, in the era of countries with lockdown, city quarantines, postponed non-obligatory clinical appointments, and curfew, the importance of the shift of health-care services to virtual environment increased. In this study, it was aimed to interpret the search volumes of "telepsychiatry" and "online therapy" topics, one of the telemental health services, based on Google Trends, to evaluate the health seeking behavior in society and the demand for telemental health services.

Methods: Google Trends is a free to access tool that provides relative volume of the terms that people searched in Google engine. Relative Search Volumes on two topics, Telepsychiatry and Online Counseling, were obtained through Google Trends. Search titles are used as "topics" since they represent a group of terms in any language that Google trends covers.

Results: Relative search results were evaluated as before and after the pandemic, online therapy and telepsychiatry. Comparisons that not normally distributed were assessed through Mann–Whitney U test. The search volume for telepsychiatry and online therapy after the pandemic increased significantly compared to before the pandemic ($p<0.05$). When search volumes in both before and after the pandemic were compared, interest to online therapy was superior than telepsychiatry in both periods ($p<0.05$).

Conclusion: It could be said that, in time periods like pandemics and the cases that people cannot reach conventional mental health support, if the issues in legal, ethical, technical, therapeutic relationship, and professionalism could be overcome, the interest in telemental health would increase.

INTRODUCTION

Cases of pneumonia of unknown etiology were first reported in December 2019 in Wuhan, China. The isolation of a new type of coronavirus Severe Acute Respiratory Syndrome (SARS) CoV-2 was announced by the Chinese Government in January 2020. Due to the rapidly spreading epidemic affecting the whole world, it was declared a pandemic by the World Health Organization.[1,2] Considering its contagiousness, the quantity of patients infected, and the clinical spectrum it revealed, the ongoing COVID-19 outbreak has had more serious consequences than pandemics such as pandemic influenza and the SARS.[2] With the declaration of the pandemic, several governments imposed restrictions on access to routine health services to prevent the spread of the virus and to combat the health burden caused by the virus. To reduce crowding and the risk of contamination in hospitals, guidelines have been established in our country with recommendations such as appointment-only patient admission and social distance.[3] Organizations such as the American College of Surgeons and the Centers for Medicare and Medicaid Services have both expressed concerns about postponing routine healthcare and elective surgeries.[4,5] To meet the health needs of the communities, the existing health services and policies were modified.[6,7] There have been promising research and publications that show how telehealth services help public health and reduce transmission.[7,8] It might be argued that shifting health services to the virtual world was a necessary shift in this period when many countries were implementing lockdowns, cities were under quarantine, non-essential clinical meetings were postponed and curfews were implemented.[9]

Studies on the rising prevalence of mental health problems such as anxiety, depression, and panic disorder as a result of the mandatory social isolation and stringent quarantine rules during this time, in addition to the uncertainty regarding the prevalence and risks of the contagiousness of

COVID-19, have been conducted.[10,11] In addition, it may be claimed that the pandemic caused negative emotions in people and people who are afraid of being alone socially faced with a "mental health pandemic" given the significant changes in living situations.[12] The implementation of measures to contain the pandemic, such as quarantine, social isolation, and social distancing, has affected the dynamics of social connections, including between those individuals who provide and receive mental health treatment during the pandemic.[12-16] The emergence of this pandemic in the digital age has raised the use of "telemental health" services, which include terms such as "online therapy," "online counseling," and "online psychotherapy," where interaction with a qualified psychologist or psychotherapist is provided through remote access. The above-mentioned services include telemedicine applications, telepsychiatry applications, which is a sub-title of telemedicine, and telemental health applications.[13,14,16-20]

The term infodemiology combines the concept of information with epidemiology.[21] Traditional epidemiological data gathering techniques, such as survey studies and cohort studies, require time to provide information that may be used to improve public health-related policy.[21] Infodemiology's goal is to use the electronic information's distribution and factors that influence it, particularly online or among a population, to inform public health and policy.[21] Every online search for health-related information leaves a digital footprint on the Internet.[21,22] There are studies showing that people's search patterns before seeking medical attention for health issues are indicative of their health-seeking practices.[21-24] An important goal of infodemiology research is to evaluate information and communication models that relate to epidemiological data or are useful for promoting public health and policymaking in this area.[21] In this approach, we believed that by looking at search data for the "telemental health" service globally and in our country, we might learn more about the demands and needs of the societies for these services. To the best of our knowledge, although telemental health services including telemedicine, online therapy, and online counseling are not legally regulated in Türkiye, certain private organizations, institutes, or single professionals working in the mental health sector are progressively providing telemental health services. This makes it reasonable to presume that individuals in our country and throughout the world are searching online for telemental health services.

This study aims to examine the change in the interest and demand for telemental health services during the pandemic, using the relative search volume (RSV) data obtained through Google Trends™ using the search topics "telepsychiatry" and "online therapy."

MATERIALS AND METHODS

Google Trends is an open public tool that provides the RSV that people search for in the Google search engine. Google Trends searches have "search term" and "topic" options. [24] "Search term" results for all keywords containing the selected term, while "topics" refers to a group of terms that share the same concept in any language. [21,24] It is scored from 0 to 100, and higher scores indicate more interest.[24,25] A value of 0 indicates low search volumes that were not included in the results, not that the topic was not searched.[24] Due to the global impact of the COVID-19 pandemic, "online therapy" and "telepsychiatry" topics, which search for equivalents in different languages, were used instead of "search terms." To minimize the impact of the development of technology on our study, it was thought that it would be more acceptable to base it only on the 4-year period. The date range January 01, 2018 – December 31, 2021 has been selected. To better understand the impact of the pandemic, the date range of January 1, 2018 - December 31, 2021, when access to health institutions was limited, was selected and the subject of "telepsychiatry" was put into a second evaluation. The rationale for this was that the demand for telepsychiatry services would decrease over time, as the measures taken against the pandemic would decrease over time. The reason for not making a second call when receiving "online therapy" is that such services were offered outside the hospital and in restricted areas and this service could continue independently of the process. The weekly data from Google Trends were compared under separate headings for "Worldwide" and "Türkiye" before and after March 15, 2020, which might be chosen as the date that is the closest to March 11, 2020, when a pandemic was proclaimed. Weekly RSV values were compared as opposed to daily ones since they were retrieved weekly (daily data is only available if an 8-month timeframe is chosen). The data were obtained by querying the subject headings through Google Trends on June 20, 2022, June 24, 2022, and June 25, 2022.

Although Google Trends contains personal information, it is nevertheless accessible to the general public. Use of this data is permitted without restriction. As with other research using Google Trends, no personal information was used in the study, which was also carried out without ethics committee approval.[25,26]

Statistical Evaluation

Statistics Package for the Social Sciences (SPSS V22.0) was used to conduct the study's statistical analysis (Armonk, New York, USA). According to topic headings and time periods, the RSV values' median, mean, and standard deviations were calculated. The Kolmogorov–Smirnov test was used to examine whether or not the RSV scores were regularly distributed. The Mann–Whitney U test was utilized to compare groups. The statistical significance level was determined as $p<0.05$.

Data Access and Reporting

On June 20, 2022, June 24, and June 25, 2022, the data on the search volumes by interest and region over time were

downloaded in the form of.csv files from the accessible reporting page after choosing the search topics and period on Google Trends (https://trends.google.com/trends/).

RESULTS

Comparisons of the data obtained when the topics "online therapy" and "telepsychiatry" were searched comparatively and separately in Google Trends and the relative volume averages before and after the pandemic between January 1, 2018, and December 31, 2021, in the "Worldwide" category are given in the (Tables 1 and 2). Before the pandemic, the relative volume mean of the topic "telepsychiatry" was 28.62±7.91 globally, while it was 32.32±15.31 during the pandemic. No significant difference was observed between pre- and post-pandemic telepsychiatry RSV scores between January 1, 2018, and December 31, 2021, worldwide (p=0.356) (Table 1). While the relative volume average of the "online therapy" topic was 35.01±5.80 before the pandemic, it was 64.00±10.24 during the pandemic. During the global pandemic, there was a statistically significant increase in online searches regarding online therapy (p<0.001) (Table 1). When compared before and after the pandemic in Türkiye, searches for "online treatment" subject were identified at a significant rate, similar to the rest of the world (p<0.001) (Table 3). When the RSV values for telepsychiatry were examined between January 01, 2018 and March 31, 2021, a significant difference was found (p<0.001) (Table 4). When the full 4-year period, pre-pandemic, and post-pandemic periods

Table 1. Comparison of Relative Search Volume in "World" before and after the pandemic between 01.01.2018 - 31.12.2021

RSV TYPE	Pre-pandemic	Post-pandemic		
	Mean ± SD/median	Mean ± SD/median	Z	p
RSV (Telepsychiatry)	28.62±7.91/29.00	32.32±15.31/28.50	-.923	0.356
RSV (Online therapy)	35.01±5.80/35.50	64.00±10.24/62.00	-12.358	0.000*

RSV: Relative Search Volume, SD: Standart deviation. *p<0.0001. RSV comparison of online therapy and telepsychiatry before and after the pandemic was made with the Mann-Whitney U test.

Table 2. Comparison of groups in "World" according to the period between 01.01.2018 - 31.12.2021

Period	RSV (Telepsychiatry)	RSV (Online therapy)		
	Mean ± SD/median	Mean ± SD/median	Z	p
Pre-pandemic	3.19±0.96/3.00	34.93±5.87/35.50	-13.137	0.000*
During the pandemic	4.03±4.41/3.00	63.88±10.22/61.00	-11.910	0.000*
The entire duration	3.57±3.07/3.00	48.01±16.56/42.00	-17.655	0.000*

RSV: Relative search volume, SD: Standard deviation. *p<0.000.Online therapy and telepsychiatry. RSV comparison with the Mann-Whitney U test.

Table 3. Comparison of online therapy RSV values in Turkey before and after the pandemic between 01.01.2018 - 31.12.2021

RSV TYPE	Pre-pandemic (Turkey)	Post-pandemic (Turkey)		
	Mean ± SD/median	Mean ± SD/median	Z	p
RSV (Online therapy)	8.07±6.51/5.00	32.76±18.09/31.50	-10.640	0.000*

RSV: Relative search volume, SD: Standard deviation. * p<0.0001. RSV comparison of online therapy before and after the pandemic was made with the Mann-Whitney U test.

Table 4. Comparison of telepsychiatry RSV values worldwide between 01.01.2018 and 31.03.2021 before and after the pandemic

RSV TYPE	Pre-pandemic (World)	Post-pandemic (World)		
	Mean ± SD/median	Mean ± SD/median	Z	p
RSV (telepsychiatry)	31.44±9.16/33.00	41.51±17.73/ 37.00	-3.522	0.000*

RSV: Relative search volume, SD: Standard deviation. * p<0.0001. Telepsychiatry RSV comparison with the Mann-Whitney U test.

were studied independently from the telepsychiatry RSV, the RSV of "online therapy" as a topic was significantly higher than the search volume of "telepsychiatry" globally ($p<0.001$) (Table 2). The amount of telepsychiatry searches conducted in Türkiye throughout the pre- and post-pandemic phases within the time frame we chose could not be observed due to the lack of available data. When the online therapy search volume was compared across Türkiye, the RSV was 8.07±6.51 before the pandemic and 32.76±18.09 during the pandemic. Online therapy search volume was found to be significantly higher during the pandemic in Türkiye compared to before ($p<0.001$) (Tables 1 and 3).

The search volume for online therapy was significantly higher when compared to the search volume for telepsychiatry throughout the entire period, before and after the pandemic ($p<0.001$) (Tables 2-4).

DISCUSSION

After March 2020, the start of the pandemic, search volumes indicating interest in "online therapy" and "telepsychiatry" services globally increased. The rise in this activity might be brought on by an unprecedented decrease in access to medical resources and the health workers at risk.[3,27] The fact that social isolation and quarantine have been found to be the most effective ways to slow the spread of the COVID-19, as well as the guidance of some states concerning the use of telemedicine applications to remain at home during this process, as well as their attempts to reform or loosen the laws in this area, might be additional factors that have increased interest in the field of telemental health around the globe.[6,27] As another factor explaining the rising interest in telemental health fields offering to fulfill this demand, our study findings are supported by the analysis of the steps taken to prevent the pandemic and the issues that cause individuals to seek mental health services.[10,11] Given this information, it is understandable why there has been a rising global demand for telehealth services as well as associated "telepsychiatry" and "online therapy" services.

In the area of telepsychiatry, Türkiye lacked sufficient data that allow meaningful comparison. Insufficient data can be interpreted as the interest in telepsychiatry practices in Türkiye is not sufficient. The fact that the level and suitable services are not provided to fulfill the demand of the society or that the society is unaware of these services may be one of the causes of the lack of searches in the field of telepsychiatry. Considering the indicators for the number of individuals using the Internet and households in the "Survey on Information and Communication Technology Usage in Households and by Individuals" (2020), it can be deduced that the society should have access to remote health services such as online therapy and telepsychiatry (for 2020, the households with the Internet access was 90.7%).[28] However, the pandemic has accelerated this process, rendering it inevitable that problems would arise. These factors can be categorized into three main categories, according to a review: Organizational factors (financing requirement and deployment of appropriate software, training, and workflow integration), technological factors (data privacy and access, data security, internet access and quality, availability of information technology, and high-speed internet), and social factors (the practitioner's license requirement, insurance, and reimbursement policies, as well as who is eligible for them and under what circumstances).[27] In addition to these obstacles, the belief that mental health-care professionals cannot empathize enough to provide therapeutic alliance through video conferencing; that they would not be able to recognize nonverbal cues; and that the possibility of not paying attention to details during the interview may negatively affect the patient-physician relationship may have limited the service provided in the field of telepsychiatry, preventing the demand and promotion of the field.[29,30] Although there is little interest in the field of telepsychiatry, the increase in the search data on "online therapy" in Türkiye with the pandemic can be considered as another finding that shows that people are turning to online counseling services.

The findings of our study suggest that throughout the pandemic, both internationally and in our country, there has been a rise in people searching for "online therapy." When the post-pandemic period is regarded to be 1 year, there is a significant increase in the phrase "telepsychiatry," but when the process is considered to be 2 years, there is no discernible increase. This change in the findings can be explained by the ease of access to psychiatric services, which include pharmacotherapy services, and which can also be obtained from hospitals, during the normalization process. Another reason might be that as the normalization process continues, patients or medical professionals who provide telepsychiatry services prefer face-to-face meetings.

In general, telemental health services are generally practical, readily accessible, and affordable, which offer solutions in rural regions and other places where access to health services is challenging, as well as their ability to maintain social distance, and being able to be used in situations where crowds must be avoided.[30] Considering these advantages, it can be thought that the dissemination of such practices will contribute to public health.

The Google Trends data utilized in this study are dynamic, so even if the same dates are chosen with data acquired at a different time, the RSV may be different. As a result, the results may alter when using data collected at other periods. The following conditions might be regarded as the limitations of this study: Despite comparing search data from across the world and in our country, it was unable to determine how different legal systems and cultural norms in other countries affected people's behavior while seeking health; because Google Trends does not give search data based on population characteristics, it is impossible to evaluate subgroups; since the data are released once a week, comparisons are done using the most recent week rather than the precise date of March 11. Another limita-

tion of the study is the possibility that search results may include terms other than telemental health services.

When the demand for online therapy and telepsychiatry applications is interpreted with Google Trends data, we can interpret this increasing demand, which emerged after the pandemic, as a sign that telepsychiatry applications can take their place in mental health services permanently and may be demanded if the legal, ethical, technical, therapeutic relationship, and professionalism-related problems that are incompatible with the traditional health system are resolved.

Consequently, it is plausible to think that creating future health policies in line with the digital world, as well as arranging the necessary infrastructure and educational services in light of data obtained through infodemiology approaches, would be more useful and faster.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: M.B.G., A.K.; Design: M.B.G., A.K.; Supervision: M.B.G., A.K.; Fundings: M.B.G.; Data: M.B.G., A.K.; Analysis: M.B.G., A.K.; Literature search: M.B.G., A.K.; Writing: M.B.G., A.K.; Critical revision: M.B.G., A.K.

Conflict of Interest

None declared.

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Covid-19 Pandemisinde "Online Terapi" ve "Telepsikiyatri" Konularının Google Trends Verileri Üzerinden Değerlendirilmesi

Amaç: Pandemi ilanıyla birlikte çok sayıda ülkenin kapandığı, şehirlerin karantina altına alındığı, zorunlu olmayan klinik görüşmelerin ertelendiği, sokağa çıkma yasağı olan bu dönemde sağlık hizmetlerinin sanal ortama kaymasının önemi arttı. Bu çalışmada, tele ruh sağlığı hizmetlerinden olan "telepsikiyatri" ve "online terapi" konularının Google Trends üzerinden erişilen arama hacimlerinin yorumlanarak toplumun sağlık arama davranışı ve tele ruh sağlığı hizmetlerine yönelik talebin yorumlanmasını amaçlamaktadır.

Gereç ve Yöntem: Google Trends, insanların Google motorunda aradıkları göreli terim hacmini sağlayan, herkesin erişimine açık bir araçtır. Google Trends aracılığı ile telepsikiyatri (telepsychiatry) ve online terapi (online counselling) başlıkları olan iki konu üzerinde göreli arama hacimleri elde edildi. Arama başlıkları herhangi bir dilde bir grup terimi temsil etmesi sebebi ile konu olarak kullanıldı.

Bulgular: Göreli arama hacimleri pandemi öncesi ve sonrası, online terapi ve telepsikiyatri olamak üzere değerlendirildi. Normal dağılıma uymayan göreli arama hacim karşılaştırmaları Mann-Whitney U testi ile karşılaştırıldı. Pandemi sonrası telepsikiyatri ve online terapiye yönelik arama hacmi pandemi öncesine göre anlamlı düzeyde artmıştır ($p<0.05$). Hem pandemi öncesi hem pandemi sonrası arama hacimleri karşılaştırıldığında online terapiye yönelik ilginin her iki dönemde telepsikiyatriye göre daha yüksek olduğu görüldü ($p<0.05$).

Sonuç: Yasal, etik, teknik, teropatik ilişki ve profesyonellik ile ilgili sorunların aşılması halinde pandemi gibi halk sağlığı sorunlarda ve kişilerin geleneksel yöntemlerle ruh sağlığı desteği alamayacağı durumlarda tele ruh sağlığı hizmetlerine olan ilgisinin artabileceği söylenebilir.

Anahtar Sözcükler: Google trends; infodemiyoloji; online terapi; telepsikiyatri.

SCIE DOI: 10.14744/scie.2023.33600
South. Clin. Ist. Euras. 2023;34(4):326-329

Original Article

Laparoscopic Management of Ureter Injury During Total Laparoscopic Hysterectomy

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Submitted: 31.12.2022
Revised: 08.06.2023
Accepted: 01.09.2023

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Keywords: Laparoscopy; laparoscopic hysterectomy; ureteral injury.

ABSTRACT

Objective: Iatrogenic ureteral injuries are critical consequences of pelvic and vaginal surgeries that can lead to severe morbidity and even death. Therefore, the purpose of this study was to evaluate the outcomes of primary laparoscopic repair of ureteral injuries during laparoscopic hysterectomy (LH).

Methods: Patients who underwent LH between November 2018 and October 2021 were evaluated retrospectively. Medical records of all patients with ureter injury were reviewed and their causes of injury, incidence, treatment and follow-up were evaluated.

Results: A total of five patients had ureter injury during laparoscopic surgery. All ureter injuries immediately repaired during the same operation without conversion to laparotomy or additional trochar insertion.

Conclusion: Identification of intra-operative urinary tract injury during gynecological operations allows for appropriate and immediate repair. The result of the study showed that gynecologists experienced in endoscopic surgery can successfully and effectively managed ureteral injury during laparoscopy.

INTRODUCTION

Ureteral injuries are rare and complications, such as urinoma, urinary tract infections, ureteral stenosis, and acute kidney insufficiency, and death may occur with delayed diagnosis or mismanagement.[1,2]

Ureteral injury incidence is reported in approximately 5% of oncologic surgical procedures and about 0.1–1.5% of benign gynecologic procedures.[3,4] Hysterectomy is the most commonly performed gynecological procedure for benign uterine disease.[5] Unfortunately, ureteral injury can be observed during hysterectomy due to the close course of the ureter to the cervix and uterine artery. Laparoscopic hysterectomy (LH) has become more popular and is widely accepted surgical approach due to the decrease in length of stay, reduced post-operative analgesic demand, and faster recovery over conventional methods.[6-8] A recent meta-analysis showed that there was an in-

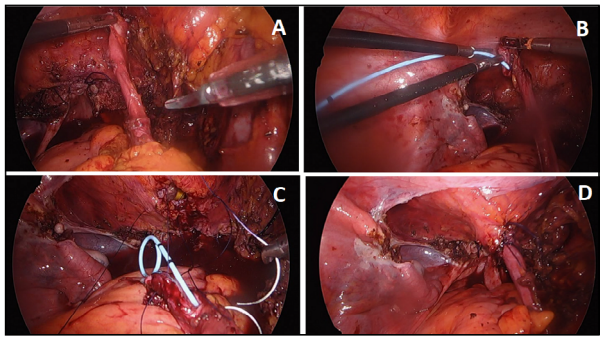

Figure 1. Intraoperative photos of the surgical technique. The ureter is dissected and released (A). The proximal and distal ureteral edges were identified, approximated by suturing at the 6 o'clock position. A double J ureteral stent was inserted in the ureter (B). 3/0 Vicryl sutures were placed at the 9, 12, and 3 o'clock positions (C). Repaired ureteral appearance (D).

creased risk of urinary tract injury in LH compared to abdominal hysterectomy.[7] It is of great importance to determine whether urological complications of laparoscopic surgeries can be properly managed with minimally invasive surgical approach. Therefore, we aimed to document the outcomes of the laparoscopic repair of ureteral injuries during gynecologic surgeries in our clinic.

MATERIALS AND METHODS

The medical records of patients who underwent LH in the Department of Obstetrics and Gynecology at the Kartal Dr. Lütfi Kırdar City Hospital, between November 2018 and October 2021 were reviewed. A total of five patients with ureteral injury during LH were identified. Patients with comorbidities (cerebrovascular disease, chronic respiratory diseases, cardiovascular disease, and coagulopathy) and previous ureteral surgery were excluded from the study. The research was in line with the principles of the Declaration of Helsinki. The ethical approval of the present study has been taken from the local ethics committee (Approval number: 2021/514/214/24, date: November 30, 2021). Following induction of anesthesia, a lithotomy position was applied to all patients. After urinary bladder catheterization, uterine manipulation was performed using a RUMI II manipulator and the vaginal cuff was closed using the intracorporeal method. The same gynecologist surgeon with extensive experience in laparoscopy performed all ureter repairs.

Surgical Techniques

Laparoscopic ureteral repair was postponed to the end of the surgery due to the possibility of further injuries. Intraoperative photos of the surgical technique are given in Figure 1. The ureters may be injured during inserting trocars or dissecting the surrounding urological structures. Ureteral injuries can be detected and managed during surgery. Laparoscopic examination revealed no bladder injuries. The ureter repair was carried out without conversion to laparotomy. There was no need to place an additional trocar during operation. The proximal and distal ureteral edges were approximated by suturing at the 6 o'clock position. After the Double-J ureteral stent application, 3/0 Vicryl sutures were placed in a clockwise order. Hemostasis was done, and an abdominal drain was implanted. The duration of catheterization was 7–10 days. All patients were monitored for 12 months after stent removal. During clinic visits, patients received a thorough work-up that included an examination of voiding symptoms, urine analysis, and ultrasonography.

RESULTS

There were five patients with iatrogenic ureteral injuries during total LH procedure over a 3-year period. There was no conversion to conventional laparoscopy during operation. The patients' mean age was 53.8 years (range: 33–66). The mean BMI was 31.7 kg/m2 (range: 25–39). The baseline characteristics of patients are presented in Table 1. The mean time of ureteral repair was 57.4 min (range: 42–80). The median duration of hospital stay was 4–7 days. Estimated blood loss was negligible. The removal

Table 1. Baseline characteristics

	Case-1	Case-2	Case-3	Case-4	Case-5
Age (year)	65	49	72	56	45
BMI (kg/m2)	28	35	26	28	29
C-Section	2	4	2	3	4
Surgery Indications	Cervical cancer	Myoma uteri	Postmenopausal bleeding	Cervical cancer	Endometrioma
Ureter Repair Time (minute)	60	42	55	50	80
Length of Hospital Stay (day)	5	4	5	7	4
Duration of Ureteral Stenting (day)	10	8	9	10	7
Complication	No	No	Urinary tract infection	Bladder atony	Urinary tract infection

BMI: Body Mass Index.

of vesical catheters and the ureteral stents was on the post-operative 7th–10th day. In the post-operative period, a catheter-associated urinary tract infection was developed in two patients and bladder atony developed in one patient. Since the catheterization lasted for a prolonged period of time, prophylactic antibiotics were used. A weekly examination of the urinary system was performed during the 1st month, followed by a monthly examination of the urinary system, a urine analysis, and a urine culture for up to 12 months. None of the patients had any pelvicalyceal ectasia. The patients had an uneventful recovery with normal renal function.

DISCUSSION

Considering the close anatomical proximity between genital and urinary structures, injury to the urinary tract, including the ureter and bladder, is a possible complication of hysterectomy.[9,10] LH is a non-invasive technique compared to abdominal hysterectomy, but a higher risk of urinary tract injury has been reported compared to abdominal or vaginal hysterectomy.[11] The probability of ureteral injury in laparoscopic operations varies between 0.2% and 6.0%. Urinary system injuries can be avoided with mastery of pelvic anatomy and surgical experience.[12]

It is important to note that ureter ligation, ureter, and bladder lacerations are acute complications, whereas vesicovaginal fistula, ureterovaginal fistula, and renal loss are chronic complications.[13] Ureteral injuries may be detected late, but in our cases, ureteral injuries were discovered and immediately repaired intraoperatively. The diagnosis and management of ureteral injuries at the time of injury reduce morbidity.[14]

Most patients with urinary tract injuries may have no risk factors. However, the risk of ureteral injury is characterized by a 2-fold increase in endometriosis cases. Apart from endometriosis, a number of pathological conditions disturb the urinary tract anatomy, which increases the risk of injury. These conditions include tubo-ovarian abscess, huge pelvic tumors, obesity, fibroids, prior surgical procedures, radiation to pelvic region, and congenital disorders of urinary tract.[15] The risk factors in our case series were leiomyoma, endometrioma, and a history of C-section, and it is hypothesized that the anatomical structural change linked with these caused ureteral damage.

A prophylactic ureteral catheter was not placed in any of our patients with ureteral injury. Feng et al.[16] showed that prophylactic ureteral catheter placement before laparoscopic gynecologic surgery, particularly in pelvic adhesions, provided benefits such as lower rate of ureteral injury, shorter length of the operation time, and less blood loss.

Urinary tract infections were developed in two cases and bladder atony in one case. However, no abnormality was found in the urinary functions of the patients in the follow-up for up to 10–12 months. This study indicated that a gynecologist or urologist with experience in minimal invasive surgery can successfully repair the injured ureters.

Conclusion

Considering the close anatomical proximity between genital and urinary structures, injury to the urinary tract, including the ureter and bladder, is a possible complication of gynecology surgery. We believe that a gynecologist or urologist with experience in minimal invasive surgery can successfully repair the injured ureters.

Ethics Committee Approval

This study approved by the Kartal Lütfi Kırdar City Hospital Clinical Research Ethics Committee (Date: 30.11.2021, Decision No: 2021/514/214/24).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: E.M., G.Y., E.K.; Design: E.K., E.M., G.Y., A.H.S.; Supervision: E.M., E.K., G.Y., P.B.İ. R.B.B.; Fundings: E.M., E.K., G.Y., U.S.; Materials: P.B.İ., R.B.B., A.H.S.; Data: P.B.İ., R.B.B., M.M.K.; Analysis: A.E., U.S., M.M.K., P.B.İ.; Literature search: M.M.K., P.B.İ., R.B.B.; Writing: P.B.İ., R.B.B., E.K., A.E.; Critical revision: G.Y., E.K. E.M., A.E.S.

Conflict of Interest

None declared.

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Total Laparoskopik Histerektomi Sırasında Üreter Yaralanmasının Laparoskopik Yönetimi

Amaç: İyatrojenik üreter yaralanmaları, ciddi morbidite ve hatta ölüme yol açabilen pelvik ve vajinal cerrahilerin kritik sonuçlarıdır. Bu nedenle, bu çalışmanın amacı laparoskopik histerektomi (LH) sırasında üreter yaralanmalarının primer laparoskopik onarımının sonuçlarını değerlendirmektir.

Gereç ve Yöntem: Kasım 2018 - Ekim 2021 tarihleri arasında LH uygulanan hastalar retrospektif olarak değerlendirildi. Üreter yaralanması olan tüm hastaların tıbbi kayıtları incelendi ve yaralanma nedenleri, insidansı, tedavisi ve takibi değerlendirildi.

Bulgular: Laparoskopik cerrahi sırasında toplam beş hastada üreter yaralanması oldu. Tüm üreter yaralanmaları laparotomiye geçilmeden veya ilave trokar yerleştirilmeden aynı ameliyatta hemen onarıldı.

Sonuç: Jinekolojik operasyonlar sırasında intraoperatif üriner sistem yaralanmasının tanımlanması, uygun ve acil onarımı sağlar. Çalışmanın sonucu, endoskopik cerrahide deneyimli jinekologların laparoskopi sırasında üreter yaralanmasını başarılı ve etkili bir şekilde yönetebileceğini gösterdi.

Anahtar Sözcükler: Laparoskopi; laparoskopik histerektomi; ureter yaralanması.

SCIE DOI: 10.14744/scie.2023.53189
South. Clin. Ist. Euras. 2023;34(4):330-334

Original Article

A Marker for Progression of Latent Tuberculosis Infection to Active Tuberculosis Infection in HIV Positive Individuals: CD4/CD8 Ratio

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Submitted: 27.10.2023
Revised: 31.10.2023
Accepted: 22.11.2023

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Keywords: Active TB Infection; CD4/CD8 Ratio; HIV; LTBI.

ABSTRACT

Objective: We aimed to determine the utility of CD4 T lymphocyte counts and percentages and CD4/CD8 ratios as markers for the progression of latent tuberculosis infection (LTBI) to active tuberculosis (TB) infection in HIV-positive patients followed in the Acquired Immunodeficiency Virus (HIV) Polyclinic of our hospital.

Methods: The files of 530 HIV-positive patients were retrospectively analyzed. "Tuberculin skin test" (TST) was applied after the anti-HIV test was positive. Asymptomatic patients with a TST ≤5 mm were considered TB negative, patients with a TST ≤5 mm were considered LTBI, and all symptomatic patients (fever, cough, night sweats, weight loss) regardless of TST result were considered as active TB infection. CD4 counts and percentages and CD4/CD8 ratios were calculated and the relationship between LTBI and active TB infection was evaluated using Mann-Whitney U test and independent sample t-test.

Results: During the specified period, 530 patients were admitted to the HIV Outpatient Clinic. There were 43 (8.11%) patients in the LTBI group, of whom 4 (9.3%) were female and 39 (90.7%) were male. CD4 was <200 mm³ in 7 (16.3%) patients and >200 mm³ in 36 (83.7%) patients. The mean CD4/CD8 ratio was 0.55 (0.08-1.45). 21 (3.96%) patients had symptoms of fever, cough, night sweats and weight loss and were diagnosed with active TB infection. Among these patients, 1 (4.8%) was female and 20 (95.2%) were male. CD4 was <200 mm³ in 5 (23.8%) patients and >200 mm³ in 16 (76.2%) patients. The mean CD4/CD8 ratio was 0.38 (0.07-1.8). The difference in CD4 counts between patients with LTBI and active TB infection was not significant, but the difference in CD4/CD8 ratio was significant ($p<0.05$).

Conclusion: Immune dysfunction that occurs in HIV and TB co-infection facilitates the activation of LTBI. While CD4 counts and CD4 percentages were not significant as risk markers, CD4/CD8 ratio was found as significant.

INTRODUCTION

We aimed to determine the demographic characteristics, prevalence of persons with latent TB infection (LTBIs) and active TB infections, CD4 T lymphocyte counts, CD4 T lymphocyte percentages, and CD4/CD8 ratios as markers for the progression of LTBI to active TB infection in 530 HIV-positive patients who were admitted to one of the HIV outpatient clinics of our hospital.

MATERIALS AND METHODS

We retrospectively evaluated 530 HIV-positive patients admitted between October 2018 and June 2023. TST (0.5 mL of purified protein derivative was administered subcutaneously in the anterior forearm, and the induration at 72 h was recorded in mm) was performed when HIV positivity was detected. Some patients were diagnosed with HIV infection after TB diagnosis. Demographic data, reasons for testing, bacillus calmette-guerin (BCG) vaccination scars, and complaints such as weight loss, fever, night sweats, and cough were recorded. Asymptomatic patients with a TST ≤5 mm were considered TB negative; patients with a TST ≤5 mm were considered LTBI; and all symptomatic patients, regardless of the TST result, were considered to have an active TB infection. Mortality rates in

LTBI and active TB infections were recorded. CD4 counts, CD4 percentages, and CD4/CD8 ratios were calculated. A Mann–Whitney U test and an independent sample t-test were used to determine the relationship between these markers and the progression of LTBI to active TB infection.

RESULTS

During this period, 530 patients were admitted to the HIV Outpatient Clinic. A total of 64 patients with TST >5 mm or complaints of fever, cough, increased sweating at night, and weight loss were included in the study because they were immunosuppressed. TST was <5 mm in 4 symptomatic patients.

43 patients (8.11%) were diagnosed with LTBI, and INH prophylaxis was initiated (Table 1). Among these patients, 4 (9.3%) were female and 39 (90.7%) were male. The mean TDT value was 10.09 (5–18) mm. Three patients had no BCG vaccination scar. 11 patients had 1, 27 patients had 2, and 2 patients had 3 BCG scars. The number of scars decreased with decreasing age. CD4 count was <200 mm³ in 7 (16.3%) patients and >200 mm³ in 36 (83.7%) patients. The mean CD4 percentage was 23.56 (7–42%) and the CD4/CD8 ratio was 0.55 (0.08–1.45). While 8 patients (18.6%) were tested due to suspicious sexual intercourse, it was detected in 5 (11.6%) patients during preoperative tests. These were followed by 4 (9.3%) patients who were examined for diarrhea and weight loss. While the CD4 count was <200 mm³ in one of these 4 patients, it was >200 mm³ in 3 of them. The other patients were diagnosed while being examined for different reasons. One patient died due to lung cancer, and another patient died due to Kaposi's sarcoma.

21 (3.96%) patients were diagnosed with active TB infection with symptoms of fever, cough, sweating, and weight loss and received quadruple anti-TB treatment (isoniazid, rifampicin, ethambutol, and pyrazinamide) (Table 1). Among these patients, 1 (4.8%) was female and 20 (95.2%) were male. The mean TDT value was 12.95 (0–30) mm. TST was <5 mm in 4 (19%) symptomatic patients. Three patients had no BCG scar. 8 patients had 1 BCG scar, 9 patients had 2 BCG scars, and 1 patient had 3 BCG scars. In this group, the number of scars was decreasing with decreasing age. CD4 count was <200 mm³ in 5 (23.8%) patients and >200 mm³ in 16 (76.2%) patients. The mean CD4 percentage was 18.42 (5–32%), and the mean CD4/CD8 ratio was 0.38 (0.07–1.8). 9 (42.8%) patients were diagnosed with HIV after the diagnosis of pulmonary TB. Seven (33.3%) patients were tested because of suspicious sexual intercourse. Four patients were diagnosed during periodic examinations at the workplace, and three patients were diagnosed after preoperative tests. Other patients were tested for different reasons. One patient with a very low CD4/CD8 ratio was diagnosed with pulmonary TB and died before cART was initiated.

CD4 counts were compared in both LTBI and active TB infection, and there was no significant difference (p=0.099).

Table 1. Demographic data of TB patients

	LTBI		Active TB Infection	
	n	%	n	%
Gender				
Male	39	90,7%	20	95,2%
Female	4	9,3%	1	4,8%
Marital status				
Single	21	48,8%	10	47,6%
Married	22	51,2%	11	52,4%
Educational status				
Primary School	16	37,2%	7	33,3%
Middle School	2	4,7%	1	4,8%
High School	12	27,9%	7	33,3%
University	13	30,2%	6	28,6%
Route of Transmission				
Sexual intercourse	42	97,7%	20	95,2%
Needle Prick	1	2,3%	0	0,0%
IV Medicine	0	0,0%	1	4,8%

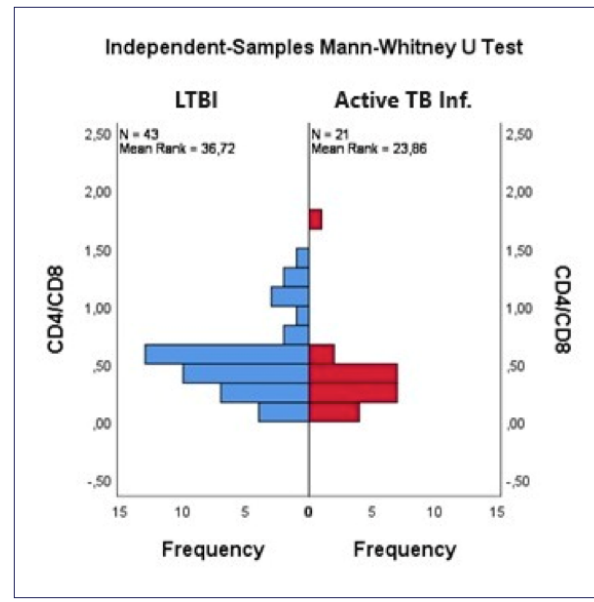

Figure 1. CD4/CD8 ratios in LTBI and Active TB Infection.

No significant difference was also found in CD4 percentages (p=0.066). When the CD4/CD8 ratios in these two groups were analyzed, it was observed that they did not exhibit a normal distribution, and nonparametric tests were applied to look for significance between the values (Figure 1). The null hypothesis was accepted as there was no significant difference in CD4/CD8 ratios between the groups. The non-parametric Mann-Whitney U test showed that the CD4/CD8 ratio was significantly higher in LTBI than in active TB infection (p<0.05).

DISCUSSION

TB is a disease caused by Mycobacterium tuberculosis

complex (M. tuberculosis, Mycobacterium bovis, Mycobacterium Africanum, and Mycobacterium microti) bacilli, which are transmitted through respiratory and droplet transmission. Although it primarily affects the lungs, it can affect any organ and can be seen in all age groups. While 95% of individuals exposed to tubercle bacilli remain LTBI, 5% progress to active TB infection in the first 2 years. In general, the risk of activation of LTBI is 5–10%.[1] TB disease, which is still an important public health problem, is the leading cause of mortality when co-infected in HIV-infected individuals.[2,3] Increasing international migration contributes to a higher incidence of HIV and TB infections in both host communities and refugees.[4,5]

HIV infection facilitates the progression of LTBI to active TB infection, independent of the CD4 T lymphocyte count.[6,7] The fact that both HIV and TB infect immune system cells mutually gives each other an advantage. M. tuberculosis ingested via aerosols is phagocytosed by macrophages in the alveoli. The macrophage environment provides a favorable environment for the bacillus to survive and grow. CD4 T lymphocytes responsible for humoral immunity and cytotoxic T lymphocytes responsible for apoptosis (CD8), which are stimulated by the activation of infected macrophages, are responsible for granuloma formation and limiting the infection.[7]

Once HIV enters the body, it infects CD4 T lymphocytes, which are its primary target cells. The functions of both TB bacilli-infected macrophages and HIV-infected CD4 T lymphocytes are affected at varying rates. Macrophage apoptosis is affected by the involvement of CD8-cytotoxic T lymphocytes. This immune impairment affects each patient differently, so the prognosis is different, and LTBI may progress to an active TB infection. The incidence of TB in HIV-positive patients is 30 times higher than in HIV-negative patients.[8] TB co-infection increases mortality more than twofold in HIV-positive patients.[9] The World Health Organization (WHO) stage III/IV, CD4 <200 mm³ and hemoglobin value <10 mg/dL have been reported as independent risk factors.[10] In this study, the CD4/CD8 ratio was determined as a risk factor rather than the CD4 count.

Among 530 HIV-positive patients, 55 (10.4%) were female and 475 (89.6%) were male. 64 (12.1%) patients were diagnosed with LTBI or active TB infection. TB is the most common infection in HIV-positive individuals. The WHO has recommended TB screening in HIV-positive patients since 2004.[11] Starting prophylaxis for LTBI after diagnosis prevents progression to active TB infection and reduces the rate of mortality.[12] 466 (87.9%) patients had a TST result of ≤5 mm, no TB symptoms, and no suspicious lesions on PA (posterior-anterior) chest radiographs; therefore, LTBI or active TB infection was not suspected.

Interleukins released from macrophages infected with M. tuberculosis stimulate CD8 cytotoxic T lymphocytes and lead to the release of interferon-gamma, which causes macrophage apoptosis.[13] Interferon gamma also plays a role in the positivity of TST, which is a type IV hypersensitivity reaction. The stimulating effect of M. tuberculosis-infected macrophages on the immune system may be impaired, especially in the acquired immunodeficiency syndrome (AIDS) presentation in which the CD4 T lymphocyte count is extremely low, and this affects the functions of CD8 T lymphocytes. In advanced AIDS patients with low CD8 T lymphocyte counts and an inability to release interferon-gamma, as in our four symptomatic patients, TST may remain negative, and imaging methods (PA chest radiography, thorax CT) may not detect TB and other infection-specific lesions in the lung parenchyma. In this condition, the patient's epidemiologic data and symptoms become important for making a diagnosis.

According to the WHO's data for 2021, 10.6 million people globally are infected with TB, which corresponds to 134 cases/100000. While 45% of cases are seen in Southeast Asia, 23% in Africa, 18% in the Western Pacific, and 8.1% in the Eastern Mediterranean.[11] Since TB infection is so common worldwide, patients with complaints such as fever, cough, weight loss, night sweats, and fatigue should be considered to have TB until proven otherwise.

A total of 64 (12.1%) patients, including 60 patients with TDT >5 mm and 4 symptomatic patients with TDT <5 mm, were included in the study. Among these patients, 5 (7.3%) were female and 59 (92.2%) were male. Forty-three (8.11%) asymptomatic patients without lung lesions were diagnosed with LTBI, and 21 (3.97%) symptomatic patients were diagnosed with active TB infection. These data suggest that HIV infection increases the prevalence of TB compared to the normal population.

The mean TST value of 43 patients diagnosed with LTBI was 10.09 (6–18). 3 patients had no BCG scar, 11 patients had 1 scar, 27 patients had 2 scars, and 2 patients had 3 scars. It was observed that as the age of the patients decreased, the number of scars decreased in parallel. The BCG vaccine limits the progression of LTBI to active TB infection and reduces the occurrence of miliary TB and TB meningitis.[14] Considering that young patients are more likely to have HIV and this group did not receive the BCG vaccine, it can be predicted that the incidence of active TB infection will increase in HIV-positive individuals. They were most frequently examined for suspected sexual intercourse, pre-operative blood donation, and generalized lymphadenomegaly. They had no complaints such as fever, cough, sweating, weight loss, weakness, or chronic diarrhea.

Seven (16.3%) patients had a CD4 count <200 mm³, while 36 (85.7%) had a CD4 count >200 mm³. Although the CD4 count was below 200 mm³, TB symptoms were not present, indicating that TB occurs independently of the CD4 count. The mean CD4 percentage was 23.56 (7–42%) and the CD4/CD8 ratio was 0.55 (0.08–1.45). One patient died of Kaposi's sarcoma, and another patient died of lung cancer. The patient with Kaposi's sarcoma was diagnosed with a CD4 count <200 mm³. This shows the correlation between CD4 count and HIV-defining malignancies.[15]

INH prophylaxis and vitamin B6 were given for 9 months

in LTBI.[16] CART was initiated on the 10th day after prophylaxis was started. Rapid initiation of cART helps the patient realize the seriousness of his or her disease, increases treatment compliance and sustainability, is effective in controlling HIV infection and reducing infectiousness, and provides a rapid increase in CD4 counts and CD4/CD8 ratio. However, delay in cART treatment may lead to the patient's loss of trust in the physician, a decrease in treatment compliance, and the continuation of infectiousness.[17] Normalization of the immune system reduces the risk of malignancy and mortality due to TB and other infections. However, the occurrence of HIV-defining malignancies is not associated with the level of CD4 alone.[15] In this study, no correlation was shown between LTBI and CD4 counts and percentages. Exacerbation and mortality were not observed in the patients. The values of patients with CD4 <200 mm³ with cART became >200 mm³ in an average of 1–6 months. Since CD4 counts and CD4/CD8 ratios were very low in 2 patients, CD4 counts exceeded 200 mm³ in the 12th month.

Active TB infection was diagnosed in 21 (3.96%) symptomatic patients, and quadruple anti-TB treatment was administered for 6 months.[18] Among these patients, 1 (4.8%) was female and 20 (95.2%) were male. TST was 0 mm (negative) in 4 patients. The mean value of TST was 12.95 (0–30) mm. This value was 2.86 mm higher than the mean value in LTBI. Three patients had no BCG scar. 8 patients had 1 BCG scar, 9 patients had 2 BCG scars, and 1 patient had 3 BCG scars. In this group, the number of BCG scars decreased with decreasing age. CD4 count was <200 mm³ in 5 (23.8%) patients and >200 mm³ in 16 (76.2%) patients. There was no significant difference compared to LTBI (p=0.099). The mean CD4 percentage was 18.42 (5–32%), which was not significant compared to LTBI (p=0.066). The mean CD4/CD8 ratio was 0.38 (0.07–1.8), which was lower than that of LTBI, and a significant difference was noted (p<0.05) (Figure 1). Patients with a low CD4/CD8 ratio had a higher risk of LTBI progression to active TB infection.

9 (42.8%) patients were diagnosed with HIV after a pulmonary TB diagnosis and had symptoms of fever, weight loss, and increased sweating at night. 12 (57.1%) patients had a TST >10 mm, and pre-cART TB treatment was initiated when they had symptoms of fever, cough, sweating, and weight loss. No patient was diagnosed with lymphoma. 7 patients were diagnosed due to suspected sexual intercourse; 4 patients were diagnosed by periodic examination at the workplace; and 3 patients were diagnosed by preoperative investigations. One patient, who started treatment for pulmonary TB, was diagnosed with HIV, had a very low CD4/CD8 ratio (0.07), and died before cART was initiated due to deterioration in general condition.

Conclusion

The most important parameter determining the prognosis of HIV infection is the CD4/CD8 ratio, and one of the treatment goals should be to increase this ratio above 0.5 or even 1. This ratio is a good marker for the progression of LTBI to active TB infection and also indicates immune damage. CD4 count and CD4 percentage are not good parameters to indicate the risk of exacerbation of LTBI.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 12.07.2023, Decision No: 2023/514/253/7).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.K., R.D.; Design: B.K., R.D.; Supervision: B.K., R.D.; Fundings: B.K., R.D.; Materials: B.K., R.D.; Data: B.K., R.D.; Analysis: B.K., R.D.; Literature search: B.K., R.D.; Writing: B.K., R.D.; Critical revision: B.K., R.D.

Conflict of Interest

None declared.

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HIV Pozitif Bireylerde Latent Tüberküloz Enfeksiyonunun Aktif Tüberküloz Enfeksiyonuna İlerlemesinde Bir Belirteç: CD4/CD8 Oranı

Amaç: Hastanemizin Edinsel İmmunyetersizlik Virüsü (HIV) Polikliniği'nde takip edilen HIV pozitif hastalardaki latent tüberküloz enfeksiyonu'nun (LTBE) aktif tüberküloz (TB) enfeksiyonuna ilerlemesinde CD4 T lenfosit sayıları ve yüzdeleri ile CD4/CD8 oranlarının bir belirteç olarak kullanılabilirliklerini öğrenmeyi amaçladık.

Gereç ve Yöntem: 530 HIV pozitif hastanın dosyaları retrospektif olarak incelendi. Hastaların anti-HIV testi pozitif geldikten sonra "tüberkülin deri testi" (TDT) uygulandı. TDT ≤5 mm olan asemptomatik hastalar TB negatif, >5 mm olan hastalar LTBE, TDT sonucundan bağımsız olarak tüm semptomatik (ateş, öksürük, gece terlemesi, kilo kaybı) hastalar aktif TB enfeksiyonu olarak kabul edildi. CD4 sayıları ve yüzdeleri ile CD4/CD8 oranları hesaplanıp, bunlarla LTBE ve aktif TB enfeksiyonu arasındaki ilişki Mann-Whitney U testi ve bağımsız örneklem t-testi uygulanarak değerlendirildi.

Bulgular: Belirtilen dönemde HIV Polikliniği'ne 530 hasta başvurdu. LTBE grubunda 43 (%8.11) hasta vardı, bunların 4'ü (%9.3) kadın, 39'u (%90.7) erkekti. Yedi (%16.3) hastada CD4 <200 mm³ iken, 36 (%83.7) hastada >200 mm³'tü. Ortalama CD4/CD8 oranı 0.55 (0.08-1.45) olarak bulundu. 21 (%3.96) hastada ateş, öksürük, gece terlemesi ve kilo kaybı semptomları vardı ve aktif TB enfeksiyonu tanısı aldı. Bu hastalardan 1'i (%4.8) kadın, 20'si (%95.2) erkek idi. Beş (%23.8) hastada CD4 <200 mm³ iken 16 (%76.2) hastada >200 mm³ idi. Ortalama CD4/CD8 oranı 0.38 (0.07-1.8) olarak saptandı. LTBE ile aktif TB enfeksiyonu arasındaki CD4 sayıları arasındaki fark anlamlı değildi fakat CD4/CD8 oranları arasındaki fark anlamlı bulundu ($p<0.05$).

Sonuç: HIV ve TB ko-enfeksiyonunda oluşan immün bozukluk LTBE'nin aktifleşmesini kolaylaştırır. Risk belirteci olarak CD4 sayıları ve CD4 yüzdeleri anlamlı değilken, CD4/CD8 oranı anlamlı bulundu.

Anahtar Sözcükler: Aktif TB enfeksiyonu; CD4/CD8 oranı; HIV; LTBE.

SCIE DOI: 10.14744/scie.2023.22599
South. Clin. Ist. Euras. 2023;34(4):335-341

Original Article

Assessment of Cardiovascular Risk Parameters in Unipolar and Bipolar Depression

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Submitted: 16.05.2023
Revised: 15.08.2023
Accepted: 16.08.2023

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Keywords: Atherogenic coefficient; atherogenic index of plasma; Castelli risk index; coronary artery disease; depression; lipid ratios.

ABSTRACT

Objective: There is strong evidence that excess and early cardiovascular disease (CVD) occurs in patients with unipolar depression (UD) and bipolar disorder - depressive episode (BD-d). The aim of this study is to evaluate plasma atherogenic index (AIP), atherogenic coefficient (AC), Castelli risk index I-II (CRI-I and II) and high-density lipoprotein (HDL) related ratios in UD, BD-d and HC.

Methods: The present study was designed as a retrospective and observational study. This study included 128 patients with UD, 184 individuals as a healthy control group and 34 patients with BD-d. AIP [log (TG/HDL)], AC [(TC-HDL)/HDL], CRI-I (TC/HDL) and II (LDL/HDL), MHR (monocyte/HDL), NHR (neutrophil/HDL), PHR (platelet/HDL) and LHR (lymphocyte/HDL) were calculated in these three groups. ANCOVA was used for age- and sex-adjusted means.

Results: There were significant differences in fasting glucose (FG) (p=0.016), LDL (p=0.004), HDL (p<0.001), TG (p<0.001), TC (p=0.01), AIP (p<0.001), NHR (p<0.001), MHR (p=0.007), LHR (p<0.001), PHR (p<0.001) between three groups. All these metabolic parameters were correlated with duration of disorder.

Conclusion: Along with the care of a depressive episode, the management of abnormal metabolic parameters should be planned during diagnosis, follow-up, and treatment. Assessment of AIP and NHR, especially in chronic and unresponsive processes, may be useful in both disorders. In future studies, it is recommended to conduct large-scale studies that are prospectively designed, that monitor the severity of the disease, and that evaluate the CVD risk parameters and treatment of the participants.

INTRODUCTION

Depression is one of the top ten leading causes of years lived with disability in the world. Major depressive disorder (MDD) ranked first, schizophrenia ranked fifth, and bipolar disorder (BD) ranked sixth in terms of disability.[1] MDD also contributed to the burden associated with ischemic heart disease and suicide.[2] There is strong evidence that adults with MDD and BD experience excess and premature cardiovascular disease (CVD). Before the use of psychotropic medications, there was an increased and early onset of CVD mortality in patients with MDD and BD, showing that the disease itself raises the risk of CVD.[3]

The frequency of metabolic syndrome (MetS) is observed at a high rate in patients with mood disorders, up to 44% of people with MDD and 37.3% of people with BD.[4] There is a high likelihood that a variety of factors are involved. These include the iatrogenic side effects of psychotropic medications, an unhealthy lifestyle, inadequate medical care for the psychiatric patient, and genetic and pathophysiological susceptibility.[5] Many lipid ratios (also known as atherogenic indices) have been shown in numerous studies to be diagnostic alternatives that can accurately predict the likelihood of CVD events and the effectiveness of treatment when conventional lipid profiles

are normal. Atherogenic index of plasma (AIP), Castelli's Risk Index I and II (CRI-I and II), atherogenic coefficient (AC), and high-density lipoprotein (HDL)-related ratios are some of them. It was shown that these ratios can help predict various CVD events.[6]

The study reported that patients with MDD had higher serum total cholesterol (TC) levels than healthy controls (HCs). When patients with MDD were compared with HCs, dysregulated lipid levels were detected in patients with MDD. In terms of lipids, patients with MDD had significantly lower TC and very low-density lipoprotein (VLDL) levels despite higher triglyceride (TG) levels. However, it was not found significant differences between HDL and LDL values in studies when patients with MDD were compared with HCs.[7] It was shown that people with BD-depressive episode (BD-d) have lower levels of TG levels than people with unipolar depression (UD).[8] Compared to patients with MDD and BD-d, HC had lower LDL and TC levels.[9] According to the baseline results of the Rehabilitation According to an Initial Schizophrenia Episode study, total duration of psychiatric illness was strongly associated with increased body mass index (BMI), and waist circumference, but not with increased metabolic parameters except for the TG to HDL ratio in the first episode schizophrenia (FES). In contrast, duration of psychotropic medication was strongly associated with lower HDL levels and systolic blood pressure, and higher non-HDL cholesterol, TG, and TG to HDL cholesterol ratio.[10] Cardiometabolic risk factors and abnormalities are seen early in the course of FES and are probably related to the underlying disease, unhealthy lifestyle, and concomitant antipsychotic use.

AIP values were the highest in patients with BD-d compared with manic, euthymic, and HCs groups. AIP levels were inversely associated with the HDL and positively associated with the MetS, waist circumference, TC, LDL, and TG levels. Patients with BD showed an increase in cardiovascular risk during a depressed episode.[11] When compared with BD-manic episode (BD-m) patients and HCs, there is no significant difference between CRI-I, CRI-II, and AC values. However, AIP levels were higher in HCs in patients with BD-m.[12] The anti-inflammatory, antioxidant, and antithrombotic effects of HDL are significant, and it has the ability to block cytokine-induced production of endothelial cell adhesion protein.[13] In patients who had coronary artery disease, monocyte to HDL ratio (MHR) was found to be independently associated with coronary atherosclerosis.[14] Lymphocyte-to-HDL ratio (LHR) and neutrophil-to-HDL ratio (NHR) may become important markers with strong predictive potential for MetS, especially in women.[15]

MetS is more common in patients with psychiatric problems. This increased risk is caused by a complex network of mechanisms that work together to negatively influence the progression of psychiatric illness. MetS needs to be identified early and prevented. As mentioned above, lipid and hematological indicators can be potential inflammatory predictors of MetS, and these parameters are easily assessed from peripheral blood. Therefore, the aim of this study is to evaluate the association between AIP, AC, CRI-I, CRI-II, and HDL-related ratios (MHR, LHR, NHR, and PHR) in UD, BD-d, and HC.

MATERIALS AND METHODS

This study has a retrospective, observational, and descriptive design. This study included 128 patients with UD who were hospitalized at Maltepe University, Faculty of Medicine, Department of Psychiatry between 2016 and 2022. To compare the patient groups, 184 HCs were selected from people with no psychiatric diseases who presented for health screening at Maltepe University, Faculty of Medicine, Department of Family Medicine between 2020 and 2022. Data from 34 patients with Bipolar Depressive episode (BD-d) were included in the current study from a previously approved study by the Ethics Committee (Ethics Committee of Sisli Etfal Training and Research Hospital dated January 24, 2017, and decision number 745). Patients with BD-d who received a Hamilton Depression Score of 20 or above were included in the study. The diagnosis of UD and BD-d was made by an experienced psychiatrist according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The study received ethical committee approval by the Clinical Research Ethics Committee of Maltepe University Faculty of Medicine (number: 2022/900/02 date: January 19, 2022).

Participants

Participants aged 18–69 years were included. All patient records were reviewed retrospectively. Blood samples from patients admitted to the psychiatric ward for UD and BD-d were taken within 24 h of admission. Individuals with a history of alcohol and substance use disorder, hypertension, diabetes mellitus, heart disease, autoimmune or inflammatory disease, cancer, active infection, and use of medications likely to affect the immune system were excluded from the study. In the HCs group, in addition to these criteria, individuals were excluded if they were suspected of having an acute or lifetime psychiatric disorder or alcohol or substance use disorder on the basis of a routine consultation with their general practitioner. The logarithm of the molar ratio of TG to HDL is represented by the AIP, a novel lipid ratio. The two lipid ratios known as Castelli's risk indices or cardiac risk indices are CRI-I and CRI-II, which measure the ratio of TC to HDL and LDL to HDL, respectively. The ratio of non-HDL cholesterol to HDL is known as the AC.[7] NHR, LHR, MHR, and PHR were computed by dividing neutrophils, lymphocytes, monocytes, and platelets by HDL.[16]

Statistical Analyses

SPSS for Windows statistical software, version 26 (SPSS Inc., Chicago, IL, USA), was used for all statistical analyses. To describe numerical data, means and standard de-

viations were employed, and to convey categorical data, frequencies and percentages were utilized. Categorical variables were compared using the Chi-square test. The Kolmogorov–Smirnov test was used to judge the distribution's normalcy. To compare continuous variables between groups, the Kruskal–Wallis test or analysis of variance with Bonferroni post hoc analysis was utilized. Non-parametric data were compared pairwise using the Mann–Whitney U-test. The Spearman's correlation test was used to assess linear connections between variables. For age- and sex-adjusted means, analysis of covariance (ANCOVA) was utilized.

RESULTS

Data from 128 patients with UD (85 women and 43 men, 34 patients with BD-d (34 men), and 184 HCs (105 women and 79 men) participated in the study. The mean age was 42.9±10.7 years in the HC, 40.3±14.9 years in the UD, and 41.2±10.2 years in the BD-d group. It was not found any significant differences in age between the three groups (p=0.178).

It was determined significant differences in fasting glucose (FG) (p=0.016), LDL (p=0.004), HDL (p<0.001), TG (p<0.001), TC (p=0.01), AIP (p<0.001), CRI-I (p=0.038), AC (p=0.038), NHR (p<0.001), MHR (p=0.007), LHR (p<0.001), and PHR (p<0.001) between three groups. After Bonferroni correction, differences disappeared in CRI-I and AC. While evaluating the metabolic parameters of participants, age- and sex-adjusted means are shown in Table 1. Pairwise comparisons after Bonferroni correction between the groups are written in Table 2. There is a significant correlation between the total number of depressive episodes and MHR, p=0.023 (cc: −.184, n=153).

Duration of disorder in UD was 10.6±8.7 years (1–40 years) and in BD-d was 17.4±9.6 years (3–40 years). The total number of depressive episodes in UD was 5.2±1.9 (1–10). Total number of mood episodes in BD-d was 9.8±6.5 and total number of depressive episodes was 4.9±3.7 (1–15). The correlation between duration of disorder and metabolic parameters is shown in Table 3. No relationship was found with other parameters.

The patients in BD-d treated with lithium carbonate (62.9%), valproic acid (28.6%), carbamazepine (2.9%), lamotrigine (17.1%), antipsychotics (94%), and antidepressant (37.1%). We do not have any data about the treatment of patients with UD before hospitalization.

DISCUSSION

The primary result of this research is that there were significant differences in AIP, LHR, NHR, PHR, LDL, HDL, and TC when comparing HC group with UD and BD-d patients. Significant differences were found in MHR values between the HC and UD groups. No differences in CRI-I, CRI-II, and AC were found among the three groups. All these metabolic parameters were correlated with the duration of the disorder.

Previous studies have reported mixed results on metabolic parameters between HC, UD, and BD-d. Some researchers reported no differences in TC, HDL, LDL, and TG levels between those groups.[17,18] According to the other studies, TG was higher, and HDL was lower in pa-

Table 1. Descriptive and metabolic parameters of participants

	Unipolar Depression (n=128) mean±SD	Bipolar Depression (n=34) mean±SD	Healthy Control (n=184) mean±SD	p	Test Statistic (F)
Sex (n-%)					
(male)	43- 33.6%	34 – 100%	79 – 42.9%		
Age (years)	40.3±14.9	41.2±10.2	42.9±10.7	0.178	1.734
FG (mg/dL)	102.06±1.62	92.68±3.1	97.6±1.24	0.016**	4.203
LDL (mg/dL)	123.107±3.78	110.31±7.24	133.36±2.91	0.004**	5.647
HDL (mg/dL)	46.85±1.23	47.25±2.36	54.79±0.95	<0.001*	15.043
TG (mg/dL)	149.42±8.71	181.69±16.68	118.49±6.7	<0.001*	8.539
TC (mg/dL)	201.03±4.11	189.89±7.8	211.87±3.16	0.010**	4.657
AIP	0.44±0.02	0.51±0.05	0.28±0.02	<0.001*	14.49
CRI- I	4.58±0.14	4.70±0.27	4.18±0.11	0.038**	3.292
CRI- II	2.82±0.11	2.77±0.22	2.66±0.08	0.570	0.563
AC	3.58±0.14	3.70±0.27	3.18±0.11	0.038**	3.292
NHR	99.72±4.26	110.02±8.20	82.30±3.29	<0.001*	8.505
MHR	13.91±0.56	14.27±1.07	11.93±0.43	0.007*	5.036
LHR	57.39±2.24	65.02±4.31	49.17±1.73	<0.001*	8.439
PHR	5628±190.04	6007.03±365.27	4833.57±146.69	<0.001*	8.340

FG: fasting glucose; LDL: low-density lipoprotein; HDL: high density lipoprotein; TG: triglyceride; TC: total cholesterol; NHR: neutrophil/HDL; MHR: monocytes/HDL; LHR: lymphocyte/HDL; PHR: platalet/HDL; AIP: Aterogenic Index Plasma; CRI-I: Castelli Index I; CRI-II: Castelli Index II; AC: Aterogenic Coeffient. Age- and sex-adjusted means were written. *: p≤0.001, **: <0.05.

Table 2. Pairwase comparisons between the groups

	Healthy Control vs. Unipolar Depression	Healthy Control vs. Bipolar Depression	Unipolar Depression vs. Bipolar Depression	N
AIP	<0.001*	<0.001*	0.820	333
CRI-I	0.091	0.245	1.000	335
CRI-II	0.906	1.000	1.000	335
AC	0.091	0.245	1.000	335
MHR	0.016**	0.139	1.000	337
LHR	0.012**	0.002*	0.380	337
NHR	0.004**	0.006*	0.834*	337
PHR	0.003**	0.010*	1.000	337
FG	0.375	0.014**	0.219	341
LDL	0.012**	<0.001*	0.078	338
HDL	0.005**	<0.001*	<0.001*	337
TG	0.136	<0.001*	0.002**	335
TC	0.016**	0.001*	0.213	337

FG: fasting glucose; LDL: low-density lipoprotein; HDL: high density lipoprotein; TG: triglyceride; TC: total cholesterol; NHR: neutrophil/HDL; MHR: monocytes/HDL; LHR: lymphocyte/HDL; PHR: platalet/HDL; AIP: Aterogenic Index Plasma; CRI-I: Castelli Index I; CRI-II: Castelli Index II; AC: Aterogenic Coeffient. ANCOVA was used and significant values were adjusted by the Bonferroni correction for multiple tests. *: p≤0.001, **: <0.05

tients with BD-d than in patients with UD.[19] In comparison to the general population, both BD and UD patients with a current depressive episode had higher levels of FG, TC, and LDL and lower levels of HDL.[20] In the present study, TG may serve as the discriminator between the three groups. Compared to HCs, HDL was decreased in both illness groups. This may be related to the lack of physical activity that occurs in depression. In addition, the fact that all patients are in a chronic course and use mood stabilizers, antidepressants, or antipsychotics for a long time may cause a deterioration of lipid parameters when assessing the duration of the illness.

The MHR ratio was predicted as a differential descriptive value for BD-d patients compared to HCs.[16] The negative correlation of MHR with the number of depressive episodes is a remarkable finding of the present study. This finding needs re-evaluation in future studies. While comparing BD-m, BD-d, and HC, there were differences in NHR, MHR, LHR, and PHR.[16] In the present study, NHR may be said to be a state marker for BD-d and UD. Considering that LHR and NHR have been suggested as strong predictors of MetS.[15] We can suggest that PHR may be important as a metabolic parameter in addition to these two parameters in this study.

Compared to BD-d and HC, UD had significantly higher Castelli's risk scores I and II. There were no significant differences in TC, LDL, TG, and FG between UD, BD-d, and HC.[21] In another study, it is not recommended to use CRI I and CRI II as indicators of mortality in patients with myocardial infarction. In addition, these indices do not predict the severity of coronary artery disease.[22] Although there was a significant difference in LDL, HDL, and TC between the healthy group and the patients, there was no difference between the CRI-I and CRI-II values; this may be related to the insufficient number of patients or CRI-I and CRI-II may not reflect metabolic abnormality in UD and BD-d.

For both depression and BD, the AIP and AC indices were significantly elevated in patients with mood disorders compared to controls.[23] AIP could be recommended as a potential biomarker for predicting CVD events in developing countries.[24] In the present study, similar results were obtained for AIP. Physical activity lowers cardiovascular risk by several pathways, including weight loss, enhanced endothelium and immunological function, and reduced blood pressure. Those who have UD or depressed symptoms are more likely to be sedentary than those who do not have a mood disorder. The AIP score can be used to assess cardiovascular risk for both UD and BD-d.

The fronto-striatal-limbic circuit is altered in BD, UD,

Table 3. The corelation between duration of disorder and metabolic parametres

	HDL	TG	AIP	CRI-I	CRI-II	AC	LHR	MHR	NHR	PHR
Duration of Disorder (p)	0.003**	0.001*	0.001*	0.001*	0.003**	0.001*	0.006**	0.018**	0.029**	0.029**
Correlation Coeffient	-.249	.279	.282	.283	.255	.283	.232	.201	.186	.187

Sperman Correlation test was used. HDL: high density lipoprotein; TG: triglyceride; LHR: lymphocyte/HDL; MHR: monocytes/HDL; PHR: platalet/HDL; NHR: neutrophil/HDL; AIP: aterogenic index; CRI-I: castelli risk index I; CRI-II: castelli risk index II; AC: aterogenic coeffient; *: p≤0.001, **: <0.05.

and obesity, which are multisystemic disorders marked by abnormalities in the inflammatory, metabolic, and endocrine systems.[25] These syndromes are considered as two different sides of inflammation, mainly because they are affected by common inflammatory processes. In addition to adipokines (cytokines secreted by adipocytes) such as adinopectin, leptin, and resistin, changes in cytokines such as TNF-α, IL-6, and IL-1 have also been reported in MetS.[26] The satiety hormone leptin shares structural similarities with pro-inflammatory cytokines. While leptin increases Th1 cytokine secretion, it inhibits Th2 cytokine production. According to epidemiological data, those with a lifetime history of depression have elevated blood leptin levels, and those with high serum leptin levels are more likely to experience major depressive episodes over the course of 5 years.[27] Some recent studies showed that resistin concentrations in patients diagnosed with major depression are associated with BMI. In addition, it has been noted that antidepressants lower resistin levels in persons with remission.[28] They influence brain activity, inflammatory alterations, and insulin resistance, which have all been proposed as shared mechanisms for the development of MetS and mood disorders.[25] In a study suggesting that ischemia-modified albumin (IMR) value can predict metabolic risk in patients with BD, unipolar disorder, and schizophrenia, the relationship of IMR with oxidative stress was emphasized and it was suggested that disease process and MetS may have a common physiopathology, especially in BD.[29] We can interpret the AIP, NHR, LHR, and PHR values as an indication of increased metabolic and cardiovascular risk for both BD-d and UD. Factors such as drug use and sedentary lifestyle alone cannot explain why these values are higher in patients. The pathophysiology of UD and BD-d may be similar to that of MetS. The need to monitor both processes simultaneously is supported by the fact that there is a negative association between disease duration and HDL and a positive association with all other metabolic markers. Treatment of metabolic abnormalities and promotion of physical activity should be included in the management of depression.

When depressed patients were divided into obese and non-obese groups, it was found that the obese group had more depressive episodes and an increased risk of recurrence.[30] In the current study, only a significant relationship was found between the number of depressive episodes and MHR. However, metabolic parameters other than HDL were positively associated with the duration of the illness, suggesting that the chronicity of depression can be assessed by means of metabolic parameters.

The main limitation of the study is its retrospective design. The fact that the severity of depression in the patients could not be assessed using a scale is another important limitation. Although the fact that the patients with BD-d included only male participants made the evaluation difficult, ANCOVA was used to remove the gender effect in the analysis. We did not have sufficient data on the treatment of patients with UD before hospitalization is another limiting factor. The lack of assessment of participants' MetS parameters, such as height, weight, BMI, waist circumference, and arterial blood pressure, may have been insufficient to assess the validity of these new metabolic parameters.

Conclusion

Our study is one of the first to evaluate all the new metabolic parameters in both UD and BD-d. Our findings suggest that AIP, NHR, LHR, and PHR should be monitored in these disorders. Along with the care of a depressive episode, the management of abnormal metabolic parameters should be planned during diagnosis, follow-up, and treatment. Assessment of AIP, especially in chronic and unresponsive processes, may be useful in both disorders. In future studies, it is recommended to conduct large-scale studies that are prospectively designed, monitor disease severity, and evaluate participants' MetS parameters and treatments.

Ethics Committee Approval

This study approved by the Maltepe University Faculty of Medicine Clinical Research Ethics Committee (Date: 19.01.2022, Decision No: 2022/900/02).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.K.K., S.K., A.E.B.T., H.E.A.Ç.; Design: B.K.K., A.E.B.T., H.E.A.Ç.; Supervision: Ş.D., S.K., B.K.K.; Fundings: B.K.K., A.E.T., H.E.A.Ç.; Materials: E.Ç.K., E.S.E.; Data: E.Ç.K., E.S.E.; Analysis: B.K.K., H.E.A.Ç., A.E.B.T.; Literature search: F.Ç.K., E.S.E., Ş.D., S.K.; Writing: B.K.K., A.E.B.T., H.E.A.Ç.; Critical revision: S.K., Ş.D.

Conflict of Interest

None declared.

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Unipolar ve Bipolar Depresyonda Kardiyovasküler Risk Parametrelerinin Değerlendirilmesi

Amaç: Unipolar depresyon (UD) ve bipolar bozukluk - depresif dönem (BB-d) hastalarında erken kardiyovasküler hastalık (KVH) oluştuğuna dair güçlü kanıtlar vardır. Bu çalışmanın amacı, UD ve BD-d'de plazma aterojenik indeks (AIP), aterojenik katsayı (AC), Castelli risk indeksi I-II (CRI-I ve II) ve yüksek yoğunluklu lipoprotein (HDL) ile ilişkili oranları değerlendirmektir.

Gereç ve Yöntem: Retrospektif ve gözlemsel olarak tasarlanan bu çalışmaya 128 UD hastası, 184 sağlıklı kontrol grubu ve 34 BB-d hastası dahil edildi. AIP [log (TG/HDL)], AC [(TC-HDL)/HDL], CRI-I (TC/HDL) ve II (LDL/HDL), MHR (monosit/HDL), NHR (nötrofil/HDL), PHR (trombosit/HDL) ve LHR (lenfosit/HDL) değerleri hesaplandı. Yaş ve cinsiyete göre düzenlenmiş ortalamalar için ANCOVA kullanıldı.

Bulgular: Açlık glukozu (FG) ($p=0.016$), LDL ($p=0.004$), HDL ($p<0.001$), TG ($p<0.001$), TC ($p=0.01$), AIP ($p<0.001$), CRI-I ($p=0.038$), AC ($p=0.038$), NHR ($p<0.001$), MHR ($p=0.007$), LHR ($p<0.001$), PHR ($p<0.001$) değerleri arasında üç grup arasında anlamlı farklılık bulunmuştur. Bonferroni düzeltmesinden sonra, CRI-I ve AC'deki farklılıklar kaybolmuştur. Tüm bu metabolik parametreler hastalığın süresi ile korele idi.

Sonuç: Depresif epizodun tanısı, takibi ve tedavisi sırasında anormal metabolik parametrelerin yönetimi planlanmalıdır. AIP'nin ve NHR'nin özellikle kronik ve yanıtsız süreçlerde değerlendirilmesi her iki bozuklukta da yararlı olabilir. Gelecekteki çalışmalarda, prospektif olarak tasarlanmış, hastalığın ciddiyetini izleyen, katılımcıların KVH risk parametrelerini ve tedavilerini değerlendiren geniş ölçekli çalışmaların yapılması önerilmektedir.

Anahtar Sözcükler: Aterojenik katsayı; aterojenik plazma indeksi; Castelli risk indeksi; koroner arter hastalığı; depresyon; lipid oranları.

SCIE DOI: 10.14744/scie.2023.46503
South. Clin. Ist. Euras. 2023;34(4):342-349

Original Article

Comparison of Psychological and Pharmacological Premedication by Assessing Preoperative Anxiety Level in Patients Scheduled for Elective Operation

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Submitted: 27.09.2023
Revised: 24.10.2023
Accepted: 25.10.2023

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Keywords: Premedication, preoperative anxiety, STAI.

ABSTRACT

Objective: This study aimed to compare the effectiveness of preoperative information and sedative premedication for decreasing preoperative anxiety of patients scheduled for elective surgery.

Methods: ASAI-II, aged 20–65 years, 90 patients who were scheduled for surgery in a University Hospital, Gynaecology and Obstetrics Service were included in the study. Anxiety levels of all patients were measured with the STAI questionnaire one day before the operation. The patients were divided into three groups. After the questionnaire, detailed private information was given to a group of patients (GroupP) by the anaesthesiologist who will perform the anaesthesia. Oral diazepam was given to a group of patients (GroupPh) before they came to the operating room. Routine preoperative visits were made to the patients in the control group (GroupC) after applying the questionnaire. After they were brought to the operating room, the STAI questionnaire was applied to all patients again before the surgery.

Results: Median State anxiety was 48 (23-70), median Trait anxiety was 44 (31-67) and median VAS was 50 (0-100) in all patients.After preoperative information, the state anxiety was lower significantly in GroupP ($p<0.001$).After diazepam, the state anxiety was lower significantly in Group Ph ($p<0.001$).The median state anxiety of GroupP and GroupPh that were assessed just before the surgery was lower than GroupC ($p=023$, $p=0.007$). There was no significant difference between the state anxiety of GroupP and GroupPh after the intervention ($p=0.750$).

Conclusion: It has been shown that effective use of the time allocated to patients and informing by the anaesthesiologist who will perform the anaesthesia in reducing preoperative anxiety is as effective as drug-induced premedication.

INTRODUCTION

Anxiety is an unpleasant condition that shows itself in the form of restlessness and tension that may be associated with hemodynamic indicators such as hypertension and tachycardia resulting from sympathetic, parasympathetic, and endocrine stimulation.[1] Awaiting surgery is a stressful situation for patients.[2] Although such anxiety seen in many patients undergoing elective surgery is considered an expected response, it is still an important problem for the majority of patients. The advancement of surgical techniques and the fact that the perioperative period has become safer do not reduce the anxiety level of patients.[3]

Anxiety affects vital signs such as pulse rate and blood pressure and increases sweating. It also has the potential to have an impact on patients' responses to anesthesia and analgesia,[4] induction of anesthesia, and recovery.[5] Preoperative anxiety is associated with increased postoperative pain, the need for analgesics, and extended hospitalization.[3] High-level anxiety may affect a patient's immune system and delay wound healing.[4] Considering these factors, it is important to evaluate patients in the preoperative period for anxiety.

The communication between the patients and the anesthesiologist occurs during the visit 1 day before the surgery.[6] This visit is the psychological part of preoperative medication. In recent years, the increased emphasis on day surgeries has resulted in anesthesiologists not having enough time to conduct extensive preoperative interviews with patients. This may also lead to a failure to provide patients with the necessary information about surgery and anesthesia.[3] On the other hand, the pharmacological part of preoperative preparation is made using various medications. Diazepam, a benzodiazepine, produces anxiolysis, sedation, and amnesia, depending on the dose. Diazepam has long been orally administered for preoperative sedation. Adults are given doses of 5–15 mg of diazepam for preoperative sedation.[7,8]

The "State-Trait Anxiety Inventory (STAI)" is the most commonly used technique among the subjective self-measurement tests to measure the level of anxiety in patients.[9] This inventory was developed by Spielberger.[10] Moreover, the Visual Analogue Scale (VAS) is an appropriate technique for measuring anxiety, and it is easy to apply.[5]

The aim of this study is to compare the briefing of the anesthesiologist who will perform anesthesia versus premedication with oral diazepam regarding their effect on the anxiety levels of patients who will undergo elective operation.

MATERIALS AND METHODS

Following the approval of the School of Medicine Noninterventional Clinical Trials Ethics Committee (decision number 2012/43-01 dated December 27, 2012), a total of 90 patients aged 20 to 65 who were classified as ASA I-II and scheduled for operation at the Gynecology and Obstetrics Department were included in the study.

Cancer, cerebral damage, psychiatric disorder, use of psychotropic medication, and mental retardation were exclusion criteria for our study population. Furthermore, illiterate patients and those who did not answer one or more questions on STAI were excluded from the study.

Study data were collected using the STAI I-II (State Anxiety Inventory [STAI-I], Trait Anxiety Inventory [STAI-II]) and VAS.

For VAS, a ruler consisting of a horizontal line marked 0 at the beginning and 100 at the end was prepared. The patients were asked to mark a place between 0 and 100 that best suited their anxiety level with an "x".

The questionnaire form was composed of three parts: Part 1 included demographic information, Part 2 included STAI-I and STAI-II, and Part 3 included a ruler for VAS scoring.

Patients who were eligible to be included in the study were determined once the next day's surgery list was issued, and they were divided into 3 groups through block randomization: the control group (Group C, n=30); the psychological premedication group (Group P, n=30), and pharmacological premedication group (Group PH, n=30).

The pre-anesthetic assessment of the patients was performed on the day before the surgery, as in their daily routine practice. In daily routine practice, anesthesiology residents evaluate a large number of patients in a short time and consult the relevant anesthesiologist. Besides the restricted time allocated for the assessment of one patient, these anesthesiology residents can perform anesthesia only for some of the patients they have evaluated.

After the routine pre-anesthetic assessment was completed, all study subjects were informed about the study by an investigator who had the knowledge of the fact that a questionnaire would be carried out but did not know which group the patients belonged to. Written informed consent was obtained from each patient and all patients were asked to fill out a three-part questionnaire (including State Anxiety-1, Trait Anxiety, and VAS-1).

After the conduction of the questionnaires, the patients in Group P were specifically informed by the anesthesiologist that would perform anesthesia on the surgery day. The briefing included information about the procedures to be carried out before getting to the operating room (preparation for surgery, how to transfer to the operating room, etc.) and the procedures to be applied to the patient when they arrived in the operating room (operating room environment, monitoring, etc.). The patients were asked about the issues that worried them about anesthesia applications and that they wanted to get information about, and they were given information about these issues. Questions asked by the patients were carefully answered. However, unnecessary details were avoided during the briefing. It was especially emphasized to the patients in GroupP that the anesthesiologist who individually informed them would be present during anesthesia application to the patient.

No additional briefing procedure was conducted for the patients in GroupPH. Patients were orally given diazepam (5 mg for patients weighing up to 70 kg, 7.5 mg for patients weighing more than 70 kg) approximately 45–60 min before they were brought to the operating room on the surgery day.

No additional briefing procedure was conducted for the patients in Group C.

When patients came to the operating room on the surgery day, an investigator who did not know which patient belonged to which group administered the STAI-I and VAS (State Anxiety-2, VAS-2) to all patients while they were in the preoperative waiting room. Before this questionaire only the patients in GroupP were greeted in the operating waiting room by the anesthesiologist, who individually informed them the day before.

The state anxiety score and the VAS score measured 1 day before the operation were recorded as "State Anxiety-1" and "VAS-1," respectively, while the state anxiety score and the VAS score were recorded as measured in the waiting room on the day of surgery and were called

"State Anxiety-2" and "VAS-2," respectively.

The manual scoring method was used in the calculation of the STAI score.

The scores obtained from both scales theoretically vary between 20 and 80. Greater scores show higher anxiety levels, while lower scores show low anxiety levels.

Power Analysis

In previous studies, Tasdemir et al.[11] measured the anxiety level using STAI in the preoperative period in patients undergoing surgery and determined the anxiety level determined by STAI as an average score of 40.6±11.23 in patients who did not receive any information or sedative anxiolytic medication. Using this data, the lowest number of cases in the groups in which a 5% decrease in STAI level could be determined with an alpha error (p value) of 0.05 and a working power of 99% was determined as 29. It was planned to include 30 patients in all groups in our study.

Statistical Analysis

The Statistical Package for Social Science 15.0 was used for the analysis of the study data. Continuous variables and their subgroups were represented as median, minimum, and maximum values. Frequency variables were expressed in frequencies and percentages. The Kolmogorov-Smirnov test was used to test compliance with the normal distribution. On the other hand, in the analysis of continuous, non-normally distributed variables, the Bonferonni-corrected Kruskal-Wallis test was used to compare three groups, and the Mann-Whitney U test was used for the comparison of two groups. The Wilcoxon test was used for intra-group comparisons. The Chi-square test was used in the analysis of the variables determined by counting. $p<0.05$ was considered statistically significant.

RESULTS

This study included 90 female patients aged from 20 to 65 years of age (median, 45.5). There was no significant difference between the groups regarding patients' educational status, occupation, and marital status (p=0.066, p=0.581, and p=0.601, respectively) (Table 1).

There was no statistically significant association between patients' age, educational status, occupational group, marital status, previous history of anesthesia, and the scores of State Anxiety-1, Trait Anxiety, and VAS-1 (p>0.05) (Table 2).

Considering all patients from the three groups, the median State Anxiety-1 score was calculated as 48 (23–70), the median Trait Anxiety score as 44 (31–67), and the median VAS-1 score as 50 (0–100). No statistically significant difference was observed between the groups and the scores obtained from State Anxiety-1, Trait Anxiety, and VAS-1 (p>0.05) (Table 3).

When the patients in Group C were compared in terms of their State Anxiety-1 and State Anxiety-2 scores, it was observed that the State Anxiety-2 scores were numerically higher, but the difference was not statistically significant (p=0.121). Furthermore, there was no statistically significant difference between VAS-1 and VAS-2 scores (p=0.987) (Table 3).

It was revealed when the patients in Group P were compared in terms of their State Anxiety-1 and State Anx-

Table 1. Sociodemographic characteristics of patients

	GroupK n=30	GroupP n=30	GroupF n=30	Total n=90
AGE median (min-max)	38 (25-60)	42.5 (20-65)	43.5 (24-65)	42.5 (20-65)
	n (%)	n (%)	n (%)	n (%)
Educational Status				
Illiterate	1 (1.1)	1 (1.1)	1 (1.1)	3 (3.3)
Secondary school graduate	4 (4.4)	3 (3.3)	6 (6.7)	13 (14.4)
High school graduate	9 (10)	11 (12.2)	7 (7.8)	27 (30)
University graduate	7 (7.8)	8 (8.9)	4 (4.4)	19 (21.1)
Primary school graduate	9 (10)	7 (7.8)	12 (13.3)	28 (31)
Occupation				
Homemaker	17 (18.9)	15 (16.7)	19 (21.1)	51 (56.7)
Government employee	7 (7.8)	7 (7.8)	3 (3.3)	17 (18.7)
Self-employed	2 (2.2)	3 (3.3)	2 (2.2)	7 (7.8)
Retiree	2 (2.2)	0	1 (1.1)	3 (3.3)
Worker	2 (2.2)	5 (5.6)	2 (2.2)	12 (13.3)
Marital Status				
Married	24 (26.7)	25 (27.8)	23 (25.6)	72 (80)
Single	4 (4.4)	5 (5.6)	2 (2.2)	11 (12.2)
Widowed	2 (2.2)	0	5 (5.6)	7 (7.8)

Table 2. Association of age groups, educational status, occupation, history of anaesthesia with State Anxiety-1, Trait Anxiety and VAS-1

		n	State Anxiety-1 Median (min-max)	Trait Anxiety Median (min-max)	VAS-1 Median (min-max)
Age Groups					
	20-35	31	41 (31-67)	40 (36-47)	50 (10-100)
	35-50	40	50 (35-71)	49 (23-64)	50 (15-90)
	Over 50 years of age	19	42 (36-63)	45 (36-63)	50 (10-100)
Educational Status					
	Primary school graduate	28	48 (35-71)	45 (36-63)	55 (0-90)
	Secondary school graduate	13	51 (31-64)	48 (34-60)	50 (10-100)
	High school graduate	27	49 (33-56)	44 (32-60)	50 (10-80)
	University graduate	19	49 (23-68)	42 (31-67)	50 (15-100)
	Illiterate	3	36 (32-37)	55 (50-56)	40 (40-55)
Occupation					
	Homemaker	51	49 (31-71)	47 (34-63)	50 (0-100)
	Government employee	17	48 (23-68)	40 (31-67)	65 (15-100)
	Self-employed	7	48 (32-52)	44 (33-51)	50 (10-85)
	Retiree	3	45 (45-51)	47 (43-55)	60 (40-60)
	Worker	12	49 (33-70)	45 (36-60)	60 (20-80)
Marital Status					
	Married	72	48 (23-71)	44 (31-60)	50 (0-100)
	Single	11	49 (35-68)	44 (35-67)	75 (15-100)
	Widowed	7	42 (31-66)	43 (34-63)	50 (40-80)
History of Anaesthesia	Yes	26	48 (23-71)	43.5 (31-67)	50 (0-100)
	No	64	51 (32-66)	47.5 (32-63)	50 (20-90)

iety-2 scores that the State Anxiety-2 scores were significantly lower ($p<0.001$). But no statistically significant difference was observed between VAS-1 and VAS-2 scores ($p=0.269$) (Table 3).

The patients in GroupPH were compared in terms of their State Anxiety-1 and State Anxiety-2 scores, and it was observed that the State Anxiety-2 scores were significantly lower ($p<0.001$). Moreover, when the VAS-1 and VAS-2 scores were compared, the VAS-2 scores were also found to be lower ($p=0.002$) (Table 3).

On the other hand, when GroupC and GroupP were compared, there was no significant difference between the groups in patients' State Anxiety-1 and VAS-1 scores ($p=0.118$ and $p=0.810$, respectively); however, the State Anxiety-2 scores of GroupP were lower compared to the State Anxiety-2 scores of GroupC ($p=0.023$). Nevertheless, no statistically significant difference was observed between the two groups in their VAS-2 scores ($p=0.851$) (Table 3).

When compared, no significant difference was found between Group C and Group PH regarding their State Anxiety-1 and VAS-1 scores ($p=0.242$ and $p=0.463$, respectively). Comparing State Anxiety-2 scores, the State Anxiety-2 scores of Group PH were significantly lower than those of GroupC ($p=0.07$). In the comparison of VAS-2 scores, the VAS-2 scores of Group PH were numerically lower, but the difference between the groups was not statistically significant ($p=0.110$) (Table 3).

Table 3. Distribution of Patients' State Anxiety-1, Trait Anxiety, VAS-1, State Anxiety-2, and VAS-2 Scores by Groups [median (min. and max.)]

	State Anxiety-1 Median (min-max)	Trait Anxiety Median (min-max)	VAS-1 Median (min-max)	State Anxiety-2 Median (min-max)	VAS-2 Median(min-max)
GroupC	46.5 (31-68)	44.5 (32-67)	50 (10-100)	48 (33-65)	50 (20-100)
GroupP	49 (35-64) ‡	42.5 (31-58)	50 (0-85)	42 (25-62) ‡ *	50 (0-90)
GroupPH	48.5 (23-71) ‡	48 (33-63)	50 (0-100) ‡	43 (22-67) ‡ †	42.5 (10-90) ‡

*: $p<0.05$, The difference between GroupC and GroupP is significant; Mann Whitney U test; †: $p<0.05$, The difference between GroupC and GroupPH is significant; Mann-Whitney U test; ‡: $p<0.05$, Intra-group evaluation is significant; Wilcoxon signed-rank test.

When a comparison was made between Group P and Group PH, no statistically significant difference was observed between the groups in terms of their State Anxiety-1, VAS-1, and State Anxiety-2 scores (p=0.830, p=0.548, and p=0.750, respectively). In the comparison of VAS-2 scores between GroupP and GroupPH, the VAS-2 scores of GroupPH were numerically lower, but the difference between the groups was not statistically significant (p=156) (Table 3).

DISCUSSION

In this study, we investigated the effect of psychological or pharmacological premedication on the state anxiety scores of female patients who would undergo elective surgery. STAI, which is used to measure preoperative anxiety, is referred to as the gold standard in the literature.[2,5,9] STAI was first developed as a tool for measuring the anxiety level in mean healthy people, but then it was revealed to be useful in measuring anxiety in patient groups.[9] VAS is an attractive alternative for measurement due to its ease of use.[5,12] For this reason, we decided to employ both STAI and VAS in our study. Studies in the literature suggest that the anxiety level measured in the afternoon of the day before the operation and the anxiety level measured just before the operation should be similar.[9,13] Therefore, in our study, to reveal the effect of psychological and pharmacological intervention on anxiety measured on the day before the operation, we measured the anxiety level for the second time just before the operation.

As a result, the State Anxiety-2 scores of the patients who received psychological or pharmacological support were found to be significantly lower as compared to the control group. We were able to indicate the positive effect of psychological or pharmacological intervention on state anxiety in the cases of elective surgery.

There are not many studies in the literature comparing the effects of psychological premedication and pharmacological premedication in reducing anxiety. Egbert et al.[14] evaluated the psychological effects of the preoperative visit by making a comparison with 2 mg/kg intramuscular pentobarbital and demonstrated that patients who were visited by an anesthesiologist before the operation were observed to be much calmer on the day of the operation. In our study, no significant difference was found between the STAI scores of GroupP and GroupPH. Furthermore, psychological and pharmacological interventions were not found to be superior to one another in reducing the anxiety of the patients. In the literature, there are many studies employing patient information to reduce preoperative anxiety. Leigh et al.[15] reported that the anxiety levels of patients who were informed about anesthesia by an anesthesiologist in the preoperative period were lower compared to the control group that did not receive such support. Again, in that study, Leigh et al.[15] made a comparison between the booklet prepared for the patients about anesthesia and the preoperative interview performed by the anesthesiologist and revealed that the interview was more effective in reducing anxiety. In another study, the doctor was stated as the primary source from whom the patients wish to get information.[16] In line with this information, the point we want to emphasize regarding our study is that the anesthesiologist's attention to the patient and careful information can reduce the anxiety of the patients as much as a pharmacological agent does.

It was suggested in a study investigating the effects of informing patients before the elective operation on the psychological ability of the patients to cope with the operation that information given in various forms positively affects patients' psychological coping skills. However, the authors emphasized that the information given to the patients should be suitable for the needs of the individual.[16] Lilja et al.[17] concluded that there must be a fine line between providing a patient with enough information to make a decision and giving too much information that could frighten the patient and cause further harm. In our study, the patients included in the psychological premedication group (GroupP) were visited by the anesthesiologist, who would perform anesthesia. The anesthesiologist provided patients with information about the procedures to be carried out before getting to the operating room (preparation for surgery, how to transfer to the operating room, etc.) and the procedures to be applied to the patient when they arrived at the operating room (operating room environment, monitoring, etc.). Questions asked by the patients were carefully answered. Unnecessary detail was avoided, and questions were answered through positive advice. It was especially emphasized that the anesthesiologist who informed the patients in this group would be ready in the operation room during the operation. We believe that the information provided by this method resulted in lower State Anxiety-2 scores in Group P patients compared to those of Group C patients. Moreover, we think that the fact that these patients got to know the anesthesiologist who would administer anesthesia in advance, that they were informed by that anesthesiologist in person, and that they were greeted by him/her in the operation waiting room on the day of the operation was effective in reducing the preoperative anxiety levels of GroupP patients in our study.

However, studies on preoperative briefing did not always show a difference between those who received and did not receive preoperative information about the surgery to be performed. Such controversial results might have resulted from the differences in study designs. In a study investigating the relationship between patients' knowledge levels about diagnosis, surgery, and anesthesia and their anxiety levels, it was found that having knowledge about anesthesia did not affect patients' levels of state anxiety. In this study, while 75% of the patients correctly described the surgical procedure, only 37.5% had knowledge about the anesthetic procedure. The percentage of patients who received information about the anesthetic method to be applied was found to be low.[6] In light of these data, as we

stated at the end of our study, the method and content of the information provided gain importance.

There are various studies in the literature about pharmacologically decreasing anxiety. In a study comparing the use of midazolam, diazepam, and placebo for premedication, no significant difference was found between diazepam and placebo in terms of their effect on decreasing the anxiety level, but the investigators employed the 'Hamilton Anxiety Test' and VAS to measure anxiety in this study.[18] In our study, however, a significant decrease was found in both the STAI and VAS scores of GroupPH who were given diazepam as the pharmacological preparation. Moreover, when compared with Group C who were not given diazepam, the anxiety levels of the patients in Group PH were found to be lower.

It has been indicated that in studies conducted to investigate preoperative anxiety, the level of preoperative anxiety ranged from 11% to 80%, depending on the scale used.[1,19] Most of the studies in the literature conducted to investigate preoperative anxiety employed the STAI to measure anxiety. Domar et al.[20] reported the mean preoperative state anxiety score as 45 with the STAI. Demir et al.[2] found the median preoperative state anxiety score to be 38 in female patients undergoing cardiac surgery. In the same study, the median trait anxiety score in women was reported to be 44. Kim et al.[9] found the mean preoperative state anxiety score to be 45.3 and trait anxiety to be 43.4 in women. Tasdemir et al.[11] reported the mean preoperative state anxiety score of female patients to be 48. We found that the median value for the State Anxiety-1 scores checked on the day before the operation was 48, and the median value for the trait anxiety score was 44 for all patients. This value is consistent with the results reported in other studies.[2,9,11,20]

Several studies in the literature have shown the relationship between gender and preoperative anxiety score, and it has been found that women have greater anxiety than men do in the preoperative period.[20] It is the reason why we included female patients in our study, who are normally thought to have higher anxiety scores than men.

When it comes to the relationship between age and preoperative anxiety level is examined, there are different results in the literature. However, some investigators suggested that age does not affect preoperative anxiety levels.[20,21] Shevde and Panagopoulos,[22] on the other hand, indicated lower preoperative anxiety levels in patients of advanced age. It was found in the study conducted by Taşdemir et al.[11] that the preoperative anxiety scores of the elderly group were lower than those of the young and middle-aged groups, although the difference between the age groups was not statistically significant. Demir et al.[2] found the anxiety level of the young patient group aged between 31 and 40 years of age to be higher compared to the other age groups; however, the difference was not statistically significant. Nevertheless, no significant relationship was found between age groups and anxiety scores or VAS scores in our study. However, although the difference was not statistically significant, the State Anxiety-1, trait anxiety, and VAS scores in the 35–50 age group were higher than those in the other age groups.

While some studies have reported that the greater the education level, the higher the anxiety becomes,[2,20] other have demonstrated that education does not affect the degree of anxiety.[11,22] A study reported that preoperative anxiety levels were higher in individuals who received more than 12 years of education.[9] Domar et al.[20] reported that although patients with higher education levels tended to report higher anxiety scores, their pulse rates measured at induction were significantly lower. On the other hand, we did not find any significant relationship between education level, anxiety scores, and VAS scores. Since the unknown factor will be less effective in educated patients, it can be expected that such patients will have lower anxiety. However, it should be taken into account that having detailed information on a subject may increase anxiety.

Furthermore, considering the effect of occupation on preoperative anxiety, studies did not find any correlation between occupation and anxiety.[20,22] It was noted in Demir et al.[2] that, although there was no significant difference, the frequency of anxiety was higher in the group of workers compared to other occupational groups. In the study by Tasdemir et al.,[11] however, the highest anxiety score was in the housewife group and the lowest anxiety score was in the civil servant group, but the difference between the groups were not statistically significant. In our study, although the differences was not statistically significant, the occupation group that had the highest level of anxiety was housewives and workers, and this result is consistent with two other studies conducted in Türkiye (Table 1).

There are studies showing that previous anesthesia experience is an important variable that has an impact on preoperative anxiety. In a study, anxiety levels were found to be high in patients who did not have a history of surgery.[23] On the contrary, in another study it was shown that women who had previous anesthesia and surgery histories had higher preoperative anxiety levels than women who had no previous exposure to anesthesia or surgery.[24] Some studies have suggested that anesthesia experience does not change the level of anxiety.[11,20] In our study, the anxiety levels of patients who had not received anesthesia before were found to be higher, but the difference was not statistically significant (Table 1).

The limitations of the study are the first point is detailed information. GroupP patients may not have been informed standardly since they were given verbal information during detailed information. Sometimes the information was shaped by the patients' questions. The second point is the timing of diazepam. It was planned to be given 45–60 min before being brought from the ward to the operating room, but the ward nurses may not have acted standardly in this regard.

In a systematic analysis that reviewed the documents related to preoperative anxiety published between 2001 and

2021, the studies about preoperative anxiety have made a huge leap forward since 2016. Interventions for preoperative anxiety, premedication, education, and briefing were the main topics of this research.[25] But as we mentioned before, there are not many studies in the literature comparing the effects of psychological premedication and pharmacological premedication in reducing anxiety.

In conclusion, we decided that using the time allocated for an interview with patients and providing patients with appropriate information were as effective as premedication with drugs in reducing preoperative anxiety. It is known that the time spent on patient interviews is decreasing day by day. Considering the fact that the number of studies comparing preoperative briefing and premedication practices with drugs is low, we have emphasized the importance of face-to-face interviews with patients and briefing patients in today's conditions, where time management is very important.

Ethics Committee Approval

This study approved by the Dokuz Eylul University Faculty of Medicine Ethics Committee (Date: 27.12.2012, Decision No: 2012/43-01).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Ş.T., E.G., T.A.; Design: S.Ş.T., E.G., T.A., V.H., H.E.; Supervision: S.Ş.T., E.Ş., V.H.; Fundings: S.Ş.T., E.Ş.; Materials: S.Ş.T.; Data: S.Ş.T., E.G., T.A., H.E.; Analysis: S.Ş.T., H.E., V.H.; Literature search: S.Ş.T., V.H., E.Ş; Writing: S.Ş.T., E.G.; Critical revision: S.Ş.T., E.G., V.H.

Conflict of Interest

None declared.

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Psikolojik ve Farmakolojik Premedikasyonun Elektif Operasyon Planlanan Hastalarda Preoperatif Anksiyete Düzeyi Ölçülerek Karşılaştırılması

Amaç: Anestezi hekiminin yaptığı özel bilgilendirme ile oral diazepam premedikasyonunun, elektif cerrahi hastalarında anksiyete düzeyine etkisini karşılaştırmaktır.

Gereç ve Yöntem: Üniversite hastanesi, kadın hastalıkları ve doğum servisinde operasyonu planlanan, 20–65 yaşlarındaki, ASAI-II, 90 hasta çalışmaya alındı. Operasyondan bir gün önce tüm hastaların STAI anketi ile anksiyete düzeyleri ölçüldü. Hastalar üç gruba ayrıldı. Anket uygulamasından sonra bir grup hastaya (GrupP), anestezi uygulamasında bulunacak anestezi hekimi tarafından ayrıntılı özel bilgilendirme yapıldı. Bir grup hastaya (GrupPh) ameliyathaneye gelmelerinden önce oral diazepam verildi. Kontrol grubu (GrupC) hastalarına anket uygulamasından sonar sadece rutin preoperatif vizit yapıldı. Ameliyathaneye getirildikten sonra tüm hastalara tekrar STAI anketi uygulandı.

Bulgular: Üç grubun tüm hastalarının operasyondan bir gün önce ölçülen durumluk anksiyete medyan değeri 48 (23-70), süreklilik anksiyete medyan değeri 44 (31-67), VAS medyan değeri 50 (0-100) olarak saptandı. GrupP hastalarının bilgilendirmeden sonraki anksiyete skorları anlamlı olarak daha düşüktü ($p<0.001$). GrupPh hastalarının Diazepam verildikten sonraki anksiyete skorunun anlamlı olarak daha düşük olduğu görüldü ($p<0.001$). Operasyon günü ameliyattan hemen önce ölçülen anksiyete skoru, GrupP ve GrupPh hastalarında GrupC hastalarına göre anlamlı olarak daha düşüktü (sırasıyla, $p=0.023$, $p=0.007$). GrupP ve GrupPh hastalarının anksiyete skorları arasında anlamlı bir fark saptanmadı ($p=0.750$).

Sonuç: Preoperatif anksiyeteyi azaltmada hastalara ayrılan sürenin efektif olarak kullanılmasının ve anestezi uygulayacak hekim tarafından yapılan bilgilendirmenin, ilaçla yapılan premedikasyon kadar etkili olduğu gösterildi.

Anahtar Sözcükler: Preoperatif anksiyete; premedikasyon; STAI.

SCIE DOI: 10.14744/scie.2023.57060
South. Clin. Ist. Euras. 2023;34(4):350-353

Original Article

Proliferative Effect of Erythropoietin on Endometrium of Postmenopausal Chronic Kidney Disease Patients

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Submitted: 24.07.2023
Revised: 11.09.2023
Accepted: 12.09.2023

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Keywords: Endometrium, EPO, erythropoietin.

ABSTRACT

Objective: A glycoprotein hormone called erythropoietin (EPO) regulates hematopoiesis, but also affects many other tissues, such as the human endometrium. Patients with chronic kidney disease (CKD) are frequently treated for anemia using recombinant EPO. The aim of this preliminary study was to evaluate the impact of recombinant EPO on the postmenopausal endometrium of individuals with CKD.

Methods: This prospectively designed study, non-hysterectomized postmenopausal women who were scheduled for Epoetin alpha treatment for their renal conditions in a nephrology clinic of a tertiary centre were included to the study between February 2017 and January 2018. To assess endometrial thickness measurements by transvaginal ultrasonography before (day 0) and at the 3rd, 30th and 90th days after the first EPO injections.

Results: Endometrial thicknessess of the study participants who received EPO (50-150 IU/kg/week) were 2.98±1.07 mm at day 0, 5.01±1.51 mm at day 3, 4.41±2.01 mm at day 30, and 3.79±1.42 mm at day 90. Endometrial thicknessess were significantly higher at 3rd and 30th day visits, when compared to the basal measurements and declined gradually at the 90th day (Repeated measures analysis of variance, post-hoc Tuckey's test, $p<0.01$).

Conclusion: Short term recombinant EPO treatment has a reversible proliferative effect on postmenopausal endometrium. In this study, short term reversible proliferative effect of EPO was observed and in one patient a benign endometrial polyp developed. Larger prospective studies could answer the risk of neoplasia in patients on chronic EPO treatment. Our study may contribute to the early diagnosis of endometrial hyperplasia or neoplasia by raising awareness about patients receiving EPO treatment.

INTRODUCTION

Erythropoietin (EPO) is a glycoprotein hormone that primarily regulates hematopoiesis by stimulating precursors of erythroid cell line in response to tissue hypoxia. On the other hand, EPO receptors have been found to exist in various tissues including nervous system, cardiovascular system, and reproductive organs.[1,2] It has been clearly shown that female reproductive organs can produce EPO, and signal transduction of EPO contributes to the cyclic changes in the female reproductive organs. EPO also has proliferative effect and contributes to the cyclic changes of the human endometrium.[2,3]

Anemia is a common problem among patients with chronic kidney disease (CKD), due to both insufficient EPO synthesis and destruction during hemodialysis.[4]

EPO has been widely used since 1989 in the treatment of CKD and anemia associated with end-stage renal disease.[5] Recombinant EPO injections are a common practice in nephrology clinics for those patients but possible effects of EPO on other tissues are usually neglected. In this preliminary study, the effect of recombinant EPO on the endometrium of postmenopausal CKD patients was assessed by transvaginal ultrasonography.

MATERIALS AND METHODS

In the present study, 20 non-hysterectomized postmenopausal women who were scheduled for epoetin alfa treatment for their renal conditions in a nephrology department of a tertiary center were included in the study between February 2017 and January 2018. All patients gave informed consent. This prospectively designed study was approved by the Institutional Ethics Committee (Approval number: 2016/7) and registered with the National Clinical Trials Registry (NCT #03060603). None of the patients received hormone replacement therapy and patients with any type of malignancy were excluded from the study. After enrollment, 4 patients were excluded from the study due to intracavitary mass which might affect endometrial measurements (postmenopausal endometrial thickness over 5 mm, n=1; FIGO Class II and III intramural fibroid, n=2; and intracavitary fluid, n=1) at the initial examination. 2 patients were lost to the follow-up. Data from the remaining 14 patients were analyzed.

Recombinant human EPO (Eprex®, with the license of Janssen-Cilag AG Switzerland, produced in Vetter Pharma-Fertigung GmbH and Co. KG, Germany) of 50–150 IU/kg/week, until the correction of anemia was observed. Mean EPO dose was 62.290±8.410 IU (range: 48.000–80.000 IU).

The primary outcome measure was endometrial thickness measurements by transvaginal ultrasonography before (day 0) and at the 3rd, 30th, and 90th days after the first EPO injections. Demographic and clinical data were given as mean±standard deviation or standard error. Repeated measures analysis of variance (ANOVA) with Bonferroni correction and post hoc Tukey's tests and SPSS 20.0 software program were used for the statistical analyses.

RESULTS

Demographic data of the patients were as follows: Mean age of the patients was 59.7±13.6 years (range: 34–76) and median parity was 3 (Interquartile range: 2.25). Mean body mass index was found as 25.9±4.81 kg/m2. The last menstrual period was 16.8±13.7 years ago (range 1–48).

Endometrial measurements are given in Table 1 . Mean endometrial thickness was different between measurements at days 0, 3, 30, and 90 significantly (p<0.01, ANOVA with repeated measures, post-hoc Tukey's test).

Table 1. Measurements of endometrial thickness with transvaginal ultrasonography in postmenopausal chronic renal failure on epoetin treatment. A) measurements 0, 3, 30 and 90 s after the first EPO injection (Repeated measures analysis of variance, p<0.01); B) Post-hoc analysis of the measurements.

A)		Endometrial Thickness			
	n	Min.	Max.	Mean	SD
Day 0	14	0.80	4.80	2.98	1.07
Day 3	14	3.30	7.90	5.01	1.51
Day 30	14	2.20	8.80	4.41	2.01
Day 90	14	2.00	7.60	3.79	1.42
B)		**Mean Diff.**	**p**	**95% CI**	
Day 0	Day 3	-2.029*	0.000	-2.855	-1.202
	Day 30	-1.436*	0.017	-2.655	-0.217
	Day 90	-0.807*	0.092	-1.707	0.092
Day 3	Day 3	2.029*	0.000	1.202	2.855
	Day 30	0.593	0.700	-0.503	1.689
	Day 90	1.221*	0.012	0.242	2.201
Day 30	Day 3	1.436*	0.017	0.217	2.655
	Day 30	-0.593	0.700	-1.689	0.503
	Day 90	0.629	0.623	-0.488	1.745
Day 90	Day 3	0.807	0.092	-0.092	1.707
	Day 30	-1.221*	0.012	-2.201	-0.242
	Day 90	-0.629	0.623	-1.745	0.488

*: p<0.05

All of the 14 patient's basal endometrial measurements were <5 mm. At their 3rd and/or 30th days of EPO treatment, the endometrium of five patients was measured >5 mm all of which returned below 5 mm at their 90th day visit. A benign endometrial polyp was seen at the 30th day visit of one patient which was then extirpated by hysteroscopy. Her endometrial thickness measurements were 4.8, 7.6, 8.8, and 4.4 mm at her 0, 3rd, 30th, and 90th-day visits, respectively. Measurement of only one of the 14 patients was over 5 mm at 90th day.

DISCUSSION

It has been demonstrated that EPO has physiological roles unrelated to erythropoiesis. Animal studies showed that mouse uterus expresses EPO and its receptor and produces EPO protein in an estrogen-dependent manner. In human endometrium, both EPO and EPO-R were detected in all samples of isolated epithelial cells analyzed throughout the menstrual cycle and have been suggested to play a physiological role in the endometrial proliferation.[3]

In the present study, 14 postmenopausal CKD patients who were prescribed EPO for anemia were investigated. None of these patients had abnormal finding on their basal transvaginal ultrasonographic examinations. On EPO treatment, at their 3rd and 30th day visits, endometrial thicknesses were found as significantly higher than the basal measurements and declined gradually at the 90th day (Table 1). Ovarian hormone changes, such as estrogen and progesterone during the menopausal period, cause amenorrhea and vasomotora symptoms.[6] In our study, postmenopausal women were included instead of not being a confounding factor since the menstrual cycle would have an effect on the thickness of the endometrium.

Unopposed estrogen and excessive proliferation of endometrium is the most common cause of endometrial hyperplasia and endometrioid endometrial carcinoma but transvaginal ultrasonography as the first-line screening tool for endometrial cancer in postmenopausal women without bleeding remains to be controversial.[7,8]

In this study, short-term reversible proliferative effect of EPO was observed and in one patient, a benign endometrial polyp developed. We think that our study encourages a multidisciplinary approach in postmenopausal womans with chronic renal disease as a comorbidity. On the other hand, long-term effects chronic EPO treatment remains to be investigated. Larger prospective studies could answer the risk of neoplasia in patients on chronic EPO treatment. The effect of EPO on endometrium in reproductive period is also unknown and this might open a new perspective for understanding endometrial proliferation (i.e., in infertility).

Conclusion

Short-term recombinant EPO treatment has a reversible proliferative effect on postmenopausal endometrium. Long-term effects of EPO in these patients and in those with reproductive period remain to be investigated.

Ethics Committee Approval

This study approved by the Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (Date: 28.01.2016, Decision No: FSM KEAH-KAEK 2016/7).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: P.B.İ., M.Y., A.İ.; Design: M.Y., E.A., N.T., M.A.S.; Supervision: M.Y., N.T., P.B.İ.; Fundings: M.Y.; Materials: P.B.İ., E.A., A.İ., Ma.Y.; Data: Ma.Y., A.İ., P.B.İ., M.A.S.; Analysis: P.B.İ., M.Y., A.İ., M.A.S., N.T.; Literature search: E.A., A.İ., M.Y.; Writing: P.B.İ., M.Y., Ma.Y.; Critical revision: E.A., A.İ., M.A.S., N.T., M.Y.

Conflict of Interest

None declared.

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Eritropoetin'in Postmenopozal Kronik Böbrek Yetmezliği Hastalarının Endometriyumu Üzerine Proliferatif Etkisi

Amaç: Eritropoietin (EPO), hematopoezi düzenlemenin yanı sıra insan endometriyumu da dahil olmak üzere çeşitli dokularda rol oynayan glikoprotein bir hormondur. Rekombinant EPO, kronik böbrek yetmezliği olan hastalarda anemi tedavisi için yaygın olarak kullanılmaktadır. Rekombinant EPO'nun kronik böbrek yetmezliği olan postmenapozal kadınların endometriumu üzerindeki etkisi, bu çalışmanın amacı olarak belirlendi.

Gereç ve Yöntem: Prospektif olarak tasarlanmış bu çalışmaya Şubat 2017- Ocak 2018 tarihleri arasında üçüncü basamak bir merkezin nefroloji kliniğinde renal sorunları nedeniyle eritropoetin tedavisi planlanan, histerektomi yapılmamış postmenopozal kadınlar dahil edildi. İlk EPO enjeksiyonlarından önce (0. gün) ve sonraki 3., 30. ve 90. günlerde transvajinal ultrasonografi ile endometrial kalınlık ölçümleri yapıldı.

Bulgular: 62.290±8.410 IU EPO alan 14 hastanın transvajinal endometriyal kalınlık ölçümleri 0. gün: 2.98±1.07, 3. gün: 5.01±1.51, 30. gün: 4.41±2.01 ve 90. gün: 3.79±1.42 idi. 3. ve 30. gün ziyaretlerinde endometriyal kalınlıkların bazal ölçümlere göre anlamlı olarak yüksek olduğu ve 90. günde kademeli olarak azaldığı görüldü (Tekrarlanan ölçümler varyans analizi, post-hoc Tuckey's test, $p<0.01$).

Sonuç: Sonuç olarak, kısa süreli rekombinant EPO tedavisi menopoz sonrası endometrium üzerinde geri dönüşümlü bir proliferatif etkiye sahiptir. Bu çalışmada, EPO'nun kısa vadede geri dönüşümlü proliferatif etkisi gözlenmiş ve bir hastada benign endometrial polip gelişmiştir. Daha büyük prospektif çalışmalar, kronik EPO tedavisi alan hastalarda neoplazi riskine cevap verebilir. Çalışmamız EPO tedavisi alan hastalar hakkında farkındalık yaratarak endometrial hiperplazi veya neoplazinin erken tanısına katkı sağlayabilir.

Anahtar Sözcükler: Endometrium; EPO; eritropoetin.

SCIE DOI: 10.14744/scie.2023.04207
South. Clin. Ist. Euras. 2023;34(4):354-357

Original Article

The Relationship between 3 Dimensional Measurement Ratios of Solid Thyroid Nodules and Thyroid Papillary Carsinoma: A Retrospective Cohort Study

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Submitted: 21.06.2023
Revised: 15.08.2023
Accepted: 17.08.2023

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Keywords: Papillary thyroid carcinoma; proportion; three dimensional imagings; thyroid nodule; ultrasound.

ABSTRACT

Objective: We aimed to investigate whether the ratios of craniocaudal (CC), anteroposterior (AP), and mediolateral (ML) measurements to each other are useful in diagnosing thyroid papillary carcinoma by ultrasound.

Methods: The patients who have a solid thyroid nodule on ultrasonography which were diagnosed by a histopathological examination after a trucut fine needle biopsy were included in this study. Proportions of all three dimensions to one another were recorded.

Results: A total of 173 patients with a mean age of 44.49±14.54 years were included. Of the patients included in the study, 137 (79.19%) were female and 38 (20.81%) were male. AP/ML ratio (p=0.016) and CC/ML ratio showed a significant difference between thyroid papillary carcinoma group and benign nodule groups. Furthermore, a cut-off value of 0.7 AP/ML ratio showed sensitivity and specificity of 0.667 and 0.45, respectively.

Conclusion: AP/ML ratio shows association with increased thyroid papillary carcinoma risk. CC/ML is also associated with increased risk. These rates may also contribute to clinical practice as a diagnostic tool.

INTRODUCTION

The incidence of thyroid cancer in the United States increased from 4.5 to 14.4/100,000 population.[1] Differential diagnosis of thyroid nodules can be challenging due to common thyroid diseases ranging from benign nodules to inflammatory changes.[1,2]

The ultrasound has a key role for detecting a lesion in thyroid and for evaluating significant features including margin characteristics, echogenicity, presence of microcalcifications, intranodal vascularity, and absence of peripheral halo.[3]

Behavior patterns of different thyroid cancers are not similar, and the dimensional characteristics of the associated thyroid nodules may also differ. The diagnostic value of craniocaudal (CC) dimension size and ratios of all dimension sizes to each other for the malignant conditions of thyroid are not well known. We aimed to investigate whether the ratios of CC, anteroposterior (AP), and mediolateral (ML) measurements to each other are useful in diagnosing thyroid papillary carcinoma (TPC) by ultrasound.

MATERIALS AND METHODS

Study Design

This is a single-center retrospective cohort study. This

study was conducted between January 2015 and December 20 patients diagnosed with the E04.1 ICD code (nontoxic single thyroid nodule) and similar subcodes were admitted to the radiology department of Van Yuzuncuyil University Hospital. This study was performed after the Hospital Ethics Committee approved the research (No. 2021/10-09). Records of patients admitted to the community-based hospital radiology department were evaluated.

Study Population

The demographic features, histopathologic results, and ultrasound workup of the patients were recorded. Patients with a solitary thyroid nodule with a histopathological examination result after a transcervical ultrasound-guided fine-needle biopsy were included in this study. The patients without three-dimensional size records or histopathological results, with previous surgery, malignancy or thyroiditis history, pregnancy, and those under 18 were excluded from the study.

Data Collection

All patients underwent transcervical ultrasonography using a 12 MHz linear probe on a Philips Affiniti 70 ultrasound device at supine position. ML and AP dimension sizes were measured by a horizontal approach. CC size was measured by a vertical approach (Figure 1). The proportion of all sizes (ML, AP, and CC) to each other was calculated. Figure 1 shows the dimension measurements on horizontal (A) and vertical (B) aspects of transcervical ultrasound. All ultrasounds were performed by radiologists. Patients were divided to TPC group and benign groups according to histopathologic results.

Study Outcomes

The primary outcome was to evaluate the ratios of CC, AP, and ML measurements to each other in diagnosing solid nodules containing TPC. Secondary outcome was to compare the dimension measurements and demographic features of patients with benign thyroid nodules and nodules containing TPC.

Statistical Analysis

Statistical analysis was conducted with SPSS (the Statistical Package for the Social Sciences) version 20 (IBM Corp., Chicago, IL, USA) for Windows. Descriptive statistics were presented as mean and standard deviation, median, and range (minimum and maximum). Normal distribution of the quantitative data was tested with the Kolmogorov–Smirnov test. Normally distributed quantitative variables were analyzed with Independent Samples t-test. Mann–Whitney U-test was used for the analysis of non-normally distributed quantitative variables. For comparison of categorical data, Pearson Chi-squared test and Fisher exact test were applied. Receiver operating characteristic (ROC) curve analysis and area under the curve values were calculated to determine the overall effectiveness of the variables. A $p<0.05$ was accepted statistically significant.

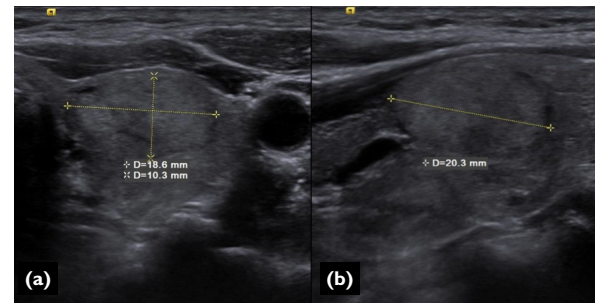

Figure 1. Anteroposterior and mediolateral dimension measurements on horizontal **(a)** and craniocaudal on vertical **(b)** aspects of transcervical ultrasound.

RESULTS

In this study, 184 patients with solid thyroid nodules were evaluated. 11 patients were excluded from the study due to other malign fine needle biopsy results. A total of 173 patients with a mean age of 44.49±14.54 years were included. Of the patients included in the study, 137 (79.19%) were female and 38 (20.81%) were male. Mean age of the male patients was 47.67±14.3. Mean age of the female patients was 43.66±14.54. There was no difference between mean age of male and female patient groups (p=0.142).

TPC rate in female group was 30/137 (22.89%). TPC rate in male group was 12/36 (33.3%). There was no significant difference between the malignancy rates of the groups (p=0.19).

AP, ML, and CC measurements showed no significant difference between the TPC and benign groups. AP, ML, and CC measurements of the benign and malign nodules are given in Table 1. AP/ML ratio showed a significant difference between TPC and benign groups (p=0.016). CC/ML ratio showed a significant difference between TPC and benign groups. AP/CC ratio had no significant difference between groups. The ratios are shown in Table 2.

ROC curve analysis of AP/ML measurement ratios showed an area under curve of 0.606 (p=0.038, 95% CI: 0.508–0.705). For a cut-off value of 0.7 AP/ML ratio, sensitivity and specificity were 0.667 and 0.45, respectively. ROC curve is shown in Figure 2. ROC curve analysis of AP/CC

Table 1. Mann Whitney U test results of Anteroposterior (AP), mediolateral (ML) and craniocaudal (CC) measurements

	ML	CC	AP
Benign			
Mean±SD	19,79±9,65	21,85+10,90	14,16+6,73
Median (min-max)	18 (5-74)	19 (8-76)	14 (4-44)
TPC			
Mean±SD	19,17±10,59	21,36+9,15	15,07+7,08
Median (min-max)	17 (8-47)	19,5 (8-45)	14,5 (6-35)
p	0,269	0,474	0,454

Table 2. Independent T-test results of anteroposterior-mediolateral, craniocaudal mediolateral and anteroposterior craniocaudal ratios are shown. (anteroposterior- mediolateral(AP/ML), craniocaudal-mediolateral(CC/ML) and anteroposterior-craniocaudal (AP/CC) ratios)

	AP/ML	CC/ML	AP/CC
Benign			
Mean±SD	0,74±0,19	1,08±0,3	0,73±0,27
TPC			
Mean±SD	0,83±0,22	1,2±0,34	0,71±0,18
p	0,021	0,043	0,135

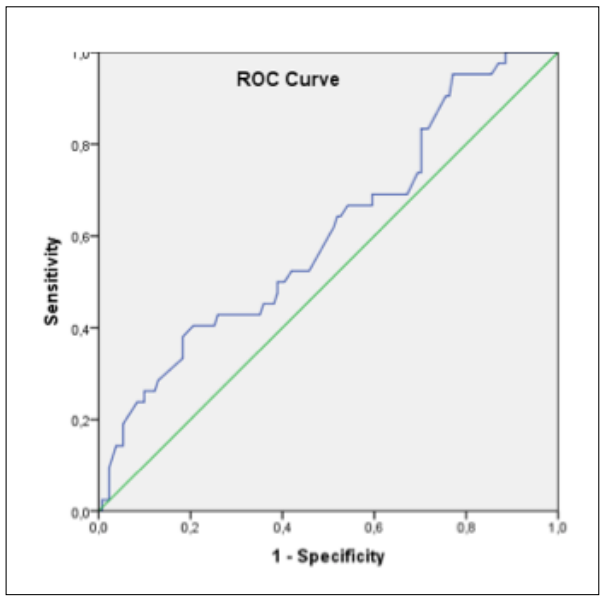

Figure 2. ROC curve of anteroposterior mediolateral measurement ratios.

measurement ratios showed an area under curve of 0.578 (p=0.127, 95% CI: 0.47–0.68).

DISCUSSION

The discrimination between benign and malign thyroid nodules is a challenge because thyroid lesions are very common in general population. Malignant lesions may be seen in relatively younger patients. Ultrasound is the most common used modality to detect nodules as well as examine the features suggestive of a malignant process.[4]

The mean size of thyroid nodules is not associated with malignancy, while irregular margin, intranodal vascularity, microcalcification, and hypoechogenic morphology were found significantly more common in malignant thyroid lesions than benign ones. Furthermore, the lesions with a craniocaudal size more than transverse (TR) size were reported with significantly higher malignancy risk.[4,5]

Previous studies concluded that AP and TR ratio (AP/TR) >1 suggests increased risk of malignancy and may be used for a criteria for recommending biopsy of a thyroid nodule.[6,7] Other studies revealed that nodules taller than wide were associated with an increased malignancy risk.[5,7] This finding is accepted as a suspicious finding in thyroid imaging reporting and data system.[8-11]

Previous studies commonly evaluated different thyroid malignancies together and investigated the differences of malign lesions from benign lesions. As one size will not fit all, different thyroid malignities may have different dimensional ratio properties. Our study tried to highlight the dimensional features of thyroid papillary carcinoma.

In our study, AP/ML ratio and CC/ML ratio showed a significant difference between TPC group and benign nodule group. Cut-off value of 0.7 AP/ML ratio showed sensitivity and specificity of 0.667 and 0.45, respectively.

The major limitations of our study are retrospective design and relatively small patient numbers in some groups. Our study focuses only on TPC. Dimensional ratio features should be evaluated for different thyroid carcinoma types.

Conclusion

Our findings suggest the association of AP/ML with increased TPC risk. CC/ML was also associated with increased risk. The nodules with higher AP dimension than ML dimension must be highlighted in the report for the increased malignancy risk.

Ethics Committee Approval

This study approved by the Van Yuzuncuyil University Ethics Committee (Date: 10.09.2021, Decision No: 2021/10-9).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: N.H., M.Ö.; Design: R.Ç., U.Ö., S.Ö.; Supervision: N.H.; Fundings: M.B.A., N.H., M.Ö.; Materials: R.Ç., S.Ö.; Data: F.D., M.B.A.; Analysis: F.D., U.Ö.; Literature search: N.H., M.Ö.; Writing: U.O., N.H., S.Ö.; Critical revision: F.D., M.B.A., S.Ö.

Conflict of Interest

None declared.

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Solid tiroid Nodüllerinin 3 Boyutlu Ölçüm Oranları ile Tiroid Papiller Karsinomunun İlişkisi: Retrospektif Kohort Çalışması

Amaç: Ultrason ile kraniokaudal, anteroposterior ve mediolateral ölçümlerin birbirine oranlarının, tiroid papiller karsinomu tanısında yararlı olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Bu çalışmaya, tru-cut ince iğne biyopsisi sonrası histopatolojik inceleme ile tanı konulan, ultrasonografide solid tiroid nodülü saptanan hastalar alındı. Her üç boyutun da birbirine oranları kaydedilerek değerlendirildi.

Bulgular: Yaş ortalaması 44.49±14.54 olan toplam 173 hasta çalışmaya dahil edildi. Çalışmaya alınan hastaların 137'si (%79.19) kadın, 38'i (%20.81) erkekti. Anteroposterior-mediolateral oran (p=0.016) ve kraniokaudal-mediolateral oran tiroid papiller karsinom grubu ile benign nodül grupları arasında anlamlı fark gösterdi. Ayrıca 0.7 AP/ML oranı kestirim değeri, sırasıyla 0.667 ve 0.45 duyarlılık ve özgüllük gösterdi.

Sonuç: AP/ML oranı, artmış tiroid papiller karsinom riski ile ilişki göstermektedir. CC/ML ayrıca artmış risk ile ilişkilidir. Bu oranlar da tanısal birer araç olarak klinik pratiğe katkı sunabilir.

Anahtar Sözcükler: Papiller tiroid karsinomu, tiroid nodülü, ultrason, üç boyutlu görüntüleme.

SCIE DOI: 10.14744/scie.2022.57983
South. Clin. Ist. Euras. 2023;34(4):358-364

Original Article

The Role of Donors' Psychological Status and Given Structured Information in Increasing Convalescent Plasma Procurement

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Submitted: 08.11.2021
Revised: 29.03.2022
Accepted: 01.04.2022

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Keywords: Pandemic; patient education; plasma donation; psychology.

ABSTRACT

Objective: Promising reports from recent studies show the effect of convalescent plasma as an adjunct alternative in treatment. The subject of our study is evaluating the current knowledge level about convalescent plasma donation and psychometric properties of possible plasma donors and their change of tendency toward being donors after receiving structured information.

Methods: Four hundred plasma donor candidates were assessed for their current knowledge level, anxiety, depression, and health anxiety scores. Their tendency to be voluntary plasma donors before and after structured information was evaluated with surveys.

Results: In participants who are undereducated or uneducated, correct information changed the decision of being a plasma donor more than educated persons, and the statistical difference between donors that have different education levels nearly disappeared with sufficient knowledge (0.006 vs. 0.037, p values). Furthermore, the previous blood donation or need for blood products in the past was important factors to be a plasma donor volunteer, regardless of sufficient information. After the structured information given, it was observed that the psychological states of the participants had no effect on plasma donation tendencies.

Conclusion: It was observed that after the correct information, the dispositional differences between the individuals disappeared, regardless of the psychological and educational status of the individuals. Furthermore, this study suggests that the previous blood donation history is a predictive factor for being a plasma donor; so, interventions to encourage blood donation are seen as an effective approach for the long-term to increase plasma donation supply in acute situations. The results of our study emphasize that informing individuals and society is one of the basic approaches to increase plasma donation in the short- and long-term.

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused a pandemic and brought about a health crisis worldwide. It has caused millions of deaths to date.[1] While scientists are continuing to develop various types of vaccines and health authorities are trying to achieve mass vaccination,[2-4] the war against the virus that causes the global health crisis continues with all available treatments.

In addition to antivirals and supportive treatments with limited efficacy in treating the disease, historical and current evidences show that human convalescent plasma therapy may be an appropriate option for alleviating and treating COVID-19 infection, especially in the early period of the disease.[5-8] The growing data we recently obtained in the COVID-19 outbreak support that the convalescent plasma can be used as an adjunct alternative in treatment.[9,10] The effect of convalescent plasma is based on the antibody response generated by recently recovered COVID-19 patients.[9] The human immune system elicits a strong antibody response from 11 to 21 days after the onset of Sars-Cov-2 infection.[11] Convalescent plasma collected from voluntary donors provides a good resource for inducing passive immunity by giving neutralizing antibodies to already infected patients.[12] Although there is

no consensus on the effectiveness of convalescent plasma in the treatment of COVID-19, promising reports from recent studies have increased clinical interest and use in the treatment.[5]

To meet the rapidly increasing plasma demand, various evaluations have been made on logistics issues such as the adequacy of blood product collection centers, processing, storage of blood products, and transportation to the place of use.[13] However, we still do not know the mechanisms and motivation behind voluntary plasma donation, which is the only source of convalescent plasma collection. In addition, the factors underlying the decision-making mechanism that affect potential plasma donors to become actual donors have not been adequately elucidated. We think that it is essential to study these factors in a patient who is just recovered from a situation that can have fatal consequences and cause direct and indirect psychological stress.

This study aims to determine the effect of the current psychological stress, level of knowledge on the subject, and previous blood product donation experiences on desiring to be a resource for plasma therapy to be used in the treatment of other patients, on people who had been sick and recovered from COVID-19 infection. In addition, it is aimed to evaluate the effect of receiving structured information on the attitude about being a donor.

MATERIALS AND METHODS

The study was carried out in our hospital between 1 and 31 February 2021. Patients who received inpatient COVID-19 treatment and recovered were included in the study as plasma donor candidates. At the first meeting with the participants, the patients' current psychological stress, their knowledge about plasma donation, their past experience of donating blood products, and their tendency to become a donor were evaluated. Afterward, structured information was given by the paramedics who were trained on plasma donation processes beforehand, and the participants' tendencies toward becoming donors were re-evaluated.

The survey was applied to 400 plasma donor candidates out of 517, who voluntarily agreed to participate and filled in survey forms. Written consent was taken from all participants, and the study was approved by the local ethics committee of the hospital.

The Structured Information, Survey, and Sociodemographic Data Form

This form was designed by the authors and applied by educated ward staff to evaluate patients' knowledge, desire to become actual plasma donors, and to record social and demographic data. The structured information was designed to educate the participants about plasma collection process, the advantages of convalescent plasma treatment in COVID-19 patients, and donation complications. Participants' thoughts about donating plasma were recorded before and after given structured information.

Hospital Depression and Anxiety Scale

14-item self-report scale,[14] each consisting of 7-question depression and anxiety subscales, scored between 0 and 3, high scores indicate increased depression and anxiety. The study's validity and reliability in Turkey have been examined.[15]

Health Anxiety Inventory

A self-report scale consisting of 18 questions,[16] the questions are scored between 0 and 3, the lowest 0 and the highest 54 points can be obtained from the scale. High scores indicate increased severity of health anxiety. The test's validity and reliability in Turkish population have been confirmed.[17]

Analytic Strategy

Statistical analyses were performed using the SPSS software version 25. To assess the normal distribution of variables, Kolmogorov–Smirnov test was used. Normally distributed variables were presented with mean±standard deviation, others presented with median (min-max). To compare the group variables, the one-way ANOVA test was used for qualitative data (Bonferroni test for post-hoc analysis) and the Chi-square test for quantitative data. The correlation coefficients and their significance were calculated using the Pearson test. Binary logistic regression was used to determine the factors predicting plasma donation behavior before and after given structured information. Values of $p<0.05$ were regarded as significant for all tests.

RESULTS

The study group consisted of 400 patients, 184 (46%) were men and 216 (54%) were women, with a mean age of 40.5±16.0 years. Twenty-six (6.5%) patients did not graduate from any school, but they were literate, the rest were graduated from primary school (%16, n=64), from high school (18.5%, n=74), and from university (59%, n=236). When their working status was examined, 316 (79%) stated that they were still working or retired from a job, 84 (21%) stated that they were not working.

The psychiatric condition of the participants was examined at the beginning of the surveys with the Hospital Depression and Anxiety Scale (HADS) and health anxiety inventory (HAI) scales. The mean HADS depression subscale score was 6.41±4.1, the HADS anxiety subscale mean score was 6.93±4.1, and the HAI total score was 16.1. According to the HADS subscales cutoff score, the presence of depression and anxiety in the participants was 198 (49.5%) and 110 (27.5%), respectively.

Before giving structured information about plasma donation to the participants; when we asked whether they were willing to donate plasma, the levels of anxiety ($F=8.842$, $p<0.01$) and health anxiety ($F=4.336$, $p=0.014$) differed statistically between the groups in the groups formed by those who said yes, no or were indecisive (Table 1). In post hoc analysis, the difference between groups was attributed

Table 1. Psychometric characteristics of groups according to plasma donation tendencies before structured information are given (n=400)

	Mean±SD			F*	p-value
	Yes	No	Indecisive		
HADS depression	6.2±4.2	5.9±3.5	7.0±4.1	0.631	0.533
HADS anxiety	7.1±3.9	2.5±3.3	7.6±4.2	8.842	<0.01**
HAI	16.5±7.7	9.6±8.6	16.6±9.2	4.336	0.014**

*F: ANOVA F value; **Significant results (p<0.05); HADS: Hospital Anxiety and Depression Scale; HAI: Health anxiety inventory; SD: Standard deviation; ANOVA: Analysis of variance.

to lower values of patients' anxiety and health anxiety levels who answered "no."

Before receiving structured information about plasma collection process and the importance of donation, 290 (72.5%) of the participants' answers were "yes," 26 (6.5%) "no," and 84 (21.0%) were "indecisive" regarding whether to donate plasma. However, after the structured information is given, the decision of 288 (72%) of the patients changed as "yes," 6 (1.5%) "no," and 106 (26.5%) "indecisive" (Table 2). The changes between the decisions before and after the given structured information were statistically significant (p<0.01). The post-hoc analysis showed that the significant difference was due to the decrease in "no" and the increase in "indecisive" answers.

Participants' knowledge level about plasma donation and their previous blood product donation experiences are shown in Table 2, and the fact that none of them had donated plasma before, but 154 (38.5%) of them donated blood previously. In the group that considered plasma donation has side effects (%40.5, n=162), most of the participants feared that the plasma donation would reduce immunity (64%, n=104). On the other side, a remarkable finding was that only a small proportion of the participants thought plasma donation was a painful procedure (10.5%, n=42) (Table 2).

Education (p<0.01) and working status (p<0.01) caused a significant difference in participants' knowledge about whether plasma donation is a painful procedure. Most of

Table 2. Participant's knowledge levels and attitudes toward donation about blood products (n=400)

	Yes, n (%)	No, n (%)	Indecisive, n (%)	χ^2 (df)	p-value
Would you accept to donate plasma?*	145 (72.5)	13 (6.5)	42 (21.0)	77.14 (4)	<0.01*
After the information, would you accept to donate plasma?*	144 (72.0)	3 (1.5)	53 (26.5)		
	Yes, n (%)			**No, n (%)**	
Do you know that convalescent plasma can be used in the treatment of active COVID-19 patients?*	161 (80.5)			39 (19.5)	
Do you know your blood group?*	177 (88.5)			23 (11.5)	
Have you donated blood before?*	77 (38.5)			123 (61.5)	
Have you or a your relative ever needed a blood donation?*	127 (63.5)			73 (36.5)	
Have you donated plasma before?*	0			200 (100)	
Are there any side effects of plasma donation?*	81 (40.5)			119 (59.5)	
Leads to fatigue (n=162)	47 (58.0)			34 (42.0)	
Leads to weight loss (n=162)	20 (24.7)			61 (75.3)	
Leads to weight gain (n=162)	15 (18.5)			66 (81.5)	
Leads to increased appetite (n=162)	18 (22.2)			63 (77.8)	
Leads to addiction (n=162)	13 (16.0)			68 (84.0)	
Leads to immunodeficiency (n=162)	52 (64.2)			29 (35.8)	
	Yes, n (%)		**No, n (%)**	**Not suren (%)**	
Does donating plasma cause pain?	21 (10.5)		83 (41.5)	96 (48.0)	

*Significant results (p<0.05).

Table 3. Classification of participant's knowledge about convalescent plasma donation according to sociodemographic characteristics (n=400)

	Donation is painful				Donation has side effects			
	Yes, n (%)	No, n (%)	χ^2 (df)	P	Yes, n (%)	No, n (%)	χ^2 (df)	p-value
Gender								
Male	58 (63.0)	34 (37.0)	1.738 (1)	0.187	41 (44.6)	51 (55.4)	1.168 (1)	0.280
Female	57 (53.8)	49 (46.2)		40 (37.0)	68 (63.0)			
Graduation								
None	12 (92.3)	1 (7.7)	25.283 (3)	<0.01*	4 (30.8)	9 (69.2)	1.643 (3)	0.650
Primary school	22 (68.8)	10 (31.2)		13 (40.6)	19 (59.4)			
High school	30 (81.1)	7 (18.9)		18 (48.5)	19 (51.4)			
College	51 (44.0)	65 (56.0)		46 (39.0)	72 (61.0)			
Working status								
Employees	83 (53.2)	73 (46.8)	7.181 (1)	0.007*	63 (39.9)	95 (60.1)	0.123 (1)	0.726
Unemployed	32 (76.2)	10 (23.8)		18 (42.9)	24 (57.1)			

*Significant results (p<0.05).

the patients who did not graduate from any school but literate thought that plasma donation was a painful process (92.3%, n=24), while this rate was 44.0% (n=102) for university graduates. The fear of experiencing pain was higher in unemployed participants than employees and retirees (76.2% vs. 53.2%) (Table 3).

Participants' tendency to be a plasma donor was examined according to sociodemographic characteristics before and after given structured information. Gender did not cause a difference in tendency to be a plasma donor before and after the information, while the education level caused statistically significant difference in both interrogations (p=0.006, 0.037, respectively). The working status caused a significant difference only before the given structured information (p=0.012) (Table 4).

Factors affecting the tendency to become plasma donors before and after the given structured information were also examined by binary logistic regression analysis. The factors affecting the willingness to donate plasma before given information were determined as; already having knowledge about the advantages of the use of convalescent plasma in COVID-19 therapy (odds ratio [OR]=13.188, %95 confidence interval [CI]=(2.95–58.8)), having donated blood before (OR=6.031, %95 CI=(1.989–18.293)), thinking that plasma donation will be painful (OR=3.858, %95 CI=(1.333–11.161)), and the higher HADS depression score (OR=1.197, %95 CI=[1.034–1.386]). Participants' willingness to donation after given information is predicted by having donated blood before (OR=3.399, %95 CI=(1.356–8.519)), having needed blood products before (OR=0.403, %95 CI=[0.174–0.935]), and knowing

Table 4. Classification of participant's attitudes about convalescent plasma donation according to sociodemographic characteristics (n=400)

	I will donate plasma (before given structured information)				I will donate plasma (after given structured information)			
	Yes, n (%)	No, n (%)	χ^2 (df)	p-value	Yes, n (%)	No, n (%)	χ^2 (df)	p-value
Gender								
Male	67 (72.8)	25 (27.2)	0.009 (1)	0.924	62 (67.4)	30 (32.6)	1.795 (1)	0.180
Female	78 (72.2)	30 (27.8)			82 (75.9)	26 (24.1)		
Graduation								
None	8 (61.5)	5 (38.5)	12.498 (3)	0.006*	11 (84.6)	2 (15.4)	8.470 (3)	0.037*
Primary school	21 (65.6)	11 (34.4)			26 (31.3)	6 (18.3)		
High school	20 (54.1)	17 (45.9)			20 (54.1)	17 (45.9)		
College	96 (81.4)	22 (18.6)			96 (81.4)	22 (18.6)		
Working status								
Employees	121 (76.6)	37 (23.4)	6.289 (1)	0.012*	121 (76.6)	37 (23.4)	1.139 (1)	0.286
Unemployed	24 (57.1)	18 (42.9)			33 (78.6)	9 (21.4)		

*Significant results (p<0.05).

Table 5. Binary logistic regression analysis of factors that may affect plasma donation attitude, before, and after given structured information plasma donation

	Before given structured information		After given structured information	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.985 (0.942–1.029)	0.501	0.967 (0.931–1.0)	0.081
Gender	0.898 (0.313–2.572)	0.841	0.741 (0.302–1.810)	0.513
Working status	0.694 (0.192–2.508)	0.578	2.879 (0.813–10.196)	0.101
To have information about the use of plasma in treatment	13.188 (2.95–58.8)	0.001*	3.079 (0.868–10.928)	0.082
To know what her/his blood type	0.285 (0.044–1.847)	0.188	0.433 (0.062–3.022)	0.399
Donating blood at least once in the past	6.031 (1.989–18.293)	0.002*	3.399 (1.356–8.519)	0.009*
Medical history of needing blood product	1.052 (0.432–2.562)	0.911	0.403 (0.174–0.935)	0.034*
Knowing that plasma donation has no side effects	1.460 (0.601–3.549)	0.404	2.262 (1.058–4.839)	0.035*
Knowing that plasma donation is not painful	3.858 (1.333–11.161)	0.013*	2.258 (0.927–5.50)	0.073
HADS depression	1.197 (1.034–1.386)	0.06	1.066 (0.946–1.201)	0.293
HADS anxiety	0.933 (0.799–1.091)	0.385	0.949 (0.828–1.0)	0.455
HAI	0.968 (0.902–1.039)	0.369	1.001 (0.941–1.064)	0.978

*Significant results (p<0.05); OR: Odds ratio; CI: Confidence interval; HADS: Hospital Anxiety and Depression Scale; HAI: Health anxiety inventory.

that plasma donation has no side effects (OR=2.262, %95 CI=[1.058–4.839]) (Table 5).

DISCUSSION

On one hand, the fight against COVID-19 is carried out with preventive health practices by trying to prevent the spread of the virus with widespread vaccination studies and social life restrictions. On the other hand, people who are not included in the vaccination program yet and, more importantly, who cannot reach vaccines globally are treated after being infected. It is known that the ideal approach in infectious diseases is to prevent the occurrence of the disease with preventive public health practices. At the point, we reached in the fight against the COVID-19 pandemic, we did not come close to this ideal since the global vaccine production capacity has not reached the level to meet the global need and the unfair distribution of vaccines in the world. It is clear that in the transition from the therapeutic approach to the preventive approach, there is still a need for development and use of all kinds of therapeutic agents. Due to the lack of definitive treatment for viral infection, in addition to existing antiviral treatments and palliative treatments, convalescent plasma collected from recovered COVID-19 patients is also tried as an additional treatment alternative. Since the one and only source of convalescent plasma is human, and its supply is based on voluntary donation, we think that it is imperative to identify the factors that may affect the decision-making process to encourage potential donors to become actual donors. From this aspect, understanding the current psychological state and knowing previous blood product donation experiences of recovered patients, and evaluating the impact of knowledge about convalescent plasma donation to become a voluntary plasma donor may be the main starting point. We showed that giving structured information by educated paramedics significantly affects our participants' decision to become a plasma donor, especially in undereducated and uneducated groups.

During the pandemic, many studies have been conducted to investigate the depression and anxiety levels of COVID-19 patients in outpatient and inpatients settings, and the reported prevalence was 19%–97% for depression and 14%–100% for anxiety.[18-20] We found 49.5% depression and 27.5% anxiety rates, consistent with the literature. Furthermore, we found that the anxiety and health anxiety scores of the groups who answered "yes-indecisive" before the given structured information was significantly higher than the group who answered "no." Although it seems paradoxical at first sight, we could argue that increased anxiety levels can increase altruism and helping behavior.[21,22] In regression analysis, we realize that, structured information given by the educated ward staff, significantly changed the influence of depression on patients' decision-making algorithm (Table 5) In participants who are less or un-educated, correct information changed the decision of being plasma donors more than educated persons. Sufficient knowledge virtually eliminated the statistical difference between education levels in the study (0.006 vs. 0.037, p values). However, in educated group, we found no significant change in tendency to become a donor with given information (Table 4). Due to the low number and proportion of participants with low education level in the sample of our study limited this promising finding. Although there is no previous study on the impact of education on plasma donation, Yildiz et al.[23] reported a similar change in people's attitude and behavior towards donating whole blood with even a brief briefing. However, considering the nature of convalescent plasma donation in a patient who has just recovered from a potentially

lethal disease, unlike a healthy person's healthy decision on donating blood, it is much more complicated and may need more knowledge in the hospital environment. While the decision to become a plasma donor before and after the information did not change according to gender, this decision differed according to the education and working status. From this aspect, our findings can guide projects to increase plasma donation rates, especially in regions with low education levels.

In regression analysis, positive answers to some of our questions ("plasma donation can be used in the treatment of COVID-19" and "plasma donation is not painful") and donating blood at least once in the past are determined as predictive factors to become a plasma donor before given information (Table 5). After given structured information, donating blood at least once in the past, medical history of needing blood product, and the knowledge about plasma donation has no side effects showing predictive value. These findings interpretable as having correct knowledge about immune plasma transfusion and its advantages in treating COVID-19 patients positively affected people's tendency to be plasma donors, regardless of their education or working status. Participants' previous blood donation experiences is determined as predictive factor to be a plasma donor volunteer, regardless of sufficient knowledge about convalescent plasma donation. To meet the increasing need for convalescent plasma during the pandemic period, we may state that inpatient education by educated staff the most effective policy in the short-term. Furthermore, social responsibility projects and campaigns about donation of blood and blood products could be beneficial to raise awareness to become plasma donors in the long-term.

Despite the encouraging results, our study has limitations, we assessed only a small inpatient group of patients, and the proportion of uneducated persons was low in our study population.

Conclusion

We showed that knowledge significantly affects our participants' decision to become a plasma donor, especially in less and uneducated group. In this point, it would not be wrong to conclude that educating potential plasma donors with even brief information by educated staffs is much more critical in developing countries or populations with low education levels.

As far as we know, this is the first study that evaluates the current knowledge level of potential convalescent plasma donors and their change of tendency toward being donors after given structured information during the SARS-CoV-2 pandemic. It was observed that after the correct information, the dispositional differences between the individuals disappeared, regardless of the psychological status and educational status of the individuals. Furthermore, the present study suggests previous blood donation history as a predictive factor for being a plasma donor; so, interventions to encourage blood donation in the long-term are looking as an effective approach to increase plasma donation supply in acute situations. The results of our study emphasize that informing individuals and society is one of the basic approaches to increase plasma donation in the short- and long-term.

Ethics Committee Approval

This study approved by the Samsun Education and Training Hospital Clinical Research Ethics Committee (Date: 01.01.2021, Decision No: GOKA2021/1/2).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: A.K.D.; Design: A.K.D., S.H.A.; Supervision: A.K.D., S.H.A., A.Ş.; Materials: S.H.A., N.G.G., A.Ş.; Data: N.G.G., A.Ş.; Analysis: A.K.D., S.H.A., N.G.G., A.Ş.; Literature search: A.K.D., S.H.A., N.G.G.; Writing: A.K.D., S.H.A.; Critical revision:A.K.D., A.Ş.

Conflict of Interest

None declared.

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Konvalesan Plazma Tedarikini Artırmada Donörlerin Psikolojik Durumlarının ve Verilen Yapılandırılmış Bilgilerin Rolü

Amaç: Son çalışmalardan elde edilen umut verici raporlar, tedavide yardımcı bir alternatif olarak konvalesan plazmanın etkisini göstermiştir. Çalışmamızın amacı, olası plazma bağışçılarının, konvalesan plazma bağışı konusunda mevcut bilgi düzeylerini, psikometrik özelliklerini ve yapılandırılmış bilgiler verildikten sonra bağışçı olma eğilimlerinin değişimini değerlendirmektir.

Gereç ve Yöntem: Dört yüz plazma bağışçısı adayı mevcut bilgi düzeyleri, kaygı, depresyon ve sağlık kaygısı puanları açısından değerlendirildi. Yapılandırılmış bilgilerden önce ve sonra gönüllü plazma bağışçısı olma eğilimleri anketlerle değerlendirildi.

Bulgular: Daha az eğitimli veya eğitimsiz katılımcılarda, doğru bilgi plazma bağışçısı olma kararını eğitimli kişilere göre daha fazla değiştirmiş ve eğitim düzeyleri arasındaki istatistiksel fark yeterli bilgi ile neredeyse ortadan kalkmıştır (0.006'ya karşı 0.037, p değerleri). Ayrıca, önceden kan bağışı yapmış olmak veya daha önce kan ürünlerine ihtiyaç duymak, yeterli bilgiye bakılmaksızın plazma bağışçısı gönüllüsü olmak için önemli faktörlerdir. Verilen yapılandırılmış bilgilerden sonra katılımcıların psikolojik durumlarının plazma bağış eğilimleri üzerinde herhangi bir etkisinin olmadığı gözlemlendi.

Sonuç: Doğru bilgi verildikten sonra bireylerin psikolojik durumları ve eğitim durumları ne olursa olsun bireyler arasındaki yatkınlık farklılıklarının ortadan kalktığı gözlemlenmiştir. Ayrıca, bu çalışmada önceki kan bağışı öyküsünün plazma bağışçısı olmak için öngörücü bir faktör olduğu sonucuna ulaşılmıştır; bu nedenle, uzun vadede kan bağışını teşvik etmeye yönelik müdahaleler, akut durumlarda plazma bağışı arzını artırmak için etkili bir yaklaşım olarak görülmektedir. Çalışmamızın sonuçları, kısa ve uzun vadede plazma bağışını artırmak için bireyleri ve toplumu bilgilendirmenin temel yaklaşımlardan biri olduğunu vurgulamaktadır.

Anahtar Sözcükler: Hasta eğitimi, pandemi, plazma bağışı, psikoloji.

SCIE DOI: 10.14744/scie.2023.45577
South. Clin. Ist. Euras. 2023;34(4):365-370

Original Article

Factors Affecting Survival in Early-Stage Lung Cancer other than Subtype and Stage

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Submitted: 31.10.2023
Revised: 09.12.2023
Accepted: 11.12.2023

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Keywords: Lobectomy; lung cancer; survival.

ABSTRACT

Objective: Main factors affecting survival in lung cancer are known to be histopathological subtype and stage. In this study, we aimed to uncover factors affecting long-term outcomes in early-stage lung cancer treated with thoracoscopic anatomical resection.

Methods: The study took place between 2006 and 2018. A total of 204 patients who underwent thoracoscopic anatomical resection were evaluated retrospectively. Preoperative, perioperative, and postoperative parameters were evaluated, and their influence on survival was analyzed. Preoperative parameters, age, gender, and respiratory function tests — diffusing capacity of the lungs for carbon monoxide (DLCO) — are evaluated. Perioperative parameters included the type of anatomical resection and conversion to open thoracotomy. Postoperative parameters included major and minor complications, duration of hospital stay.

Results: A total of 204 patients were included in the study. The 5-year survival rate was 76.5%. Age 65 or younger is related to better 5-year survival (80.6% vs. 67.7%, p=0.008). Five-year survival of patients with a DLCO value greater than 80% is 83.2%, and it is 51.1% for a DLCO value equal to or lower than 80% (p=0.001). Hospital stay for 4 days or less is related to better 5-year survival (86% vs 69%, p=0.017).

Conclusion: In our study, it was determined that age, preoperative DLCO value, duration of hospital stay, and postoperative complication development were statistically significant in survival. However, conversion to open thoracotomy and the difference between segmentectomy and lobectomy did not have a specific effect on survival.

INTRODUCTION

Among all malignancies, lung cancer is one of the deadliest. [1] Surgery is the primary treatment option in early-stage lung cancer. However, the incidence of early-stage tumors is increasing due to advancing technology, making minimally invasive surgery a subject to overriding innovations. The use of minimally invasive methods in early-stage lung cancer is on the rise.

It has been shown that the 5-year survival in early-stage lung cancer is up to 94%,[2] while the overall 5-year survival of lung cancer stands at 23.6%.[3] However, there are other factors that affect survival in early-stage lung cancer beyond stage and histopathological subtype.

In our study, the effects of preoperative, perioperative, and postoperative parameters on survival were investigated by retrospectively collecting patients who were operated on for early-stage lung cancer. Preoperative determinant factors include age, gender, forced expiratory volume in 1 second (FEV1) value, and DLCO value. Perioperative parameters include conversion to open thoracotomy, and the type of anatomical resection such as segmentectomy of lobectomy. Postoperative parameters include major complications, minor complications, and duration of hospital stay.

MATERIALS AND METHODS

Selection of Patients

After excluding benign lesions, secondary lung carcinomas, and bronchiectasis, 204 patients who underwent video-assisted thoracoscopic surgery (VATS) anatomical resec-

Table 1. Preoperative determinant factors

	Minimum	Maximum	Mean
Age	23	82	60.9±9.7
FEV1 (ml)	1030	4570	2440±705
FEV1%	%43	%146	%90.9±21.5
DLCO%	% 42	%163	%91.8±24.3
Radiological tumor size (mm)	8	90	25.5±12.1
Sex	Male: 141 (69%)	Female: 63 (31%)	
Side	Right: 120 (84%)	Left: 84 (16%)	
Preoperative tissue diagnosis	Absent: 35 (17%)	Present: 169 (83%)	

DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: Forced expiratory volume in 1 second.

tion for primary lung cancer between 2006 and 2018 were investigated retrospectively. Preoperative, perioperative, and postoperative factors were evaluated, and their influence on survival was analyzed.

Patients who met the inclusion criteria were those diagnosed with primary lung carcinoma via bronchoscopy/EBUS (Endobronchial Ultrasound) or TTFNB (Transthoracic Fine Needle Biopsy), patients operated on for a solitary pulmonary nodule and who underwent VATS anatomical resection after frozen section work-up, patients with no proven N2 disease and who did not receive neoadjuvant therapy, and patients with no suspected distant metastases via whole-body magnetic resonance imaging (MRI) or Positron Emission Tomography/Computed Tomography (PET/CT). In order to form a homogenous group, only patients who underwent thoracoscopic resection rather than open thoracotomy were included.

Ethical Considerations

This study is approved by the Ethics Committee of our Faculty by number 1347. The study procedure was prepared in accordance with the guidelines and regulations of The Code of Ethics of the World Medical Association (Declaration of Helsinki). In the study, the confidentiality of the patients was guaranteed. A detailed informed consent form was obtained from the patients prior to the operation.

Statistical Analysis

Student's T-test was preferred for parametric values, and the Mann-Whitney U test was preferred for non-parametric values for the comparison of continuous variables. The Kaplan-Meier method was used to calculate OS. Statistical significance was determined by the log-rank test. P values below 0.05 were considered to be statistically significant. Statistical analyses were performed with SPSS (Statistical Program for Social Sciences 25.0; IBM Corporation, Armonk, NY, USA).

I. Preoperative Determinant Factors

Preoperative parameters include age, gender, FEV1, and DLCO values. Preoperative parameters are shown in detail in Table 1.

II. Perioperative Determinant Factors

Segmentectomy, lobectomy, and pneumonectomy were performed on 34 (16.7%), 168 (82.8%), and 1 patient, respectively. A total of 12 patients underwent conversion. Of the 168 lobectomy procedures, 8 were VATS bronchial sleeve lobectomies.

Table 2. Distribution and rates of each complication

Complication	Number (n)	Percentage (%)
ARDS	4	2%
Chylothorax requiring re-operation	2	1%
Prolonged air leak requiring re-operation	10	4.9%
Hemorrhage requiring re-operation	1	0.5%
Atelectasis requiring bronchoscopy	4	2%
Empyema	3	1.5%
Pneumonia	30	14.7%
Atrial fibrillation	14	6.9%
Chylothorax not requiring re-operation	3	1.5%
Major Complications	24 (11.8%)	
Minor Complications	47 (23.0%)	

ARDS: Acute respiratory distress syndrome.

Table 3. Definitive histopathological diagnoses of patients

Histopathological Subtype	Count (n)	Percentage (%)
Adenocarcinoma	108	52.9
Squamous Cell Carcinoma	62	30.4
Carcinoid Tumors	18	8.8
Adenosquamous Carcinoma	8	3.9
Large Cell Carcinoma	2	1
Pleomorphic Carcinoma	3	1.5
Large Cell Neuroendocrine Tumor	3	1.5

III. Postoperative Determinant Factors

Of the 204 patients, 65% were complication-free. Complications were analyzed according to the Clavien-Dindo Classification. Atrial fibrillation, pneumonia, and chylothorax treated with a non-surgical approach belong to Clavien-Dindo grade II. Acute respiratory distress syndrome (ARDS) belongs to Clavien-Dindo grade IV. Chylothorax requiring re-operation and prolonged air leak requiring re-operation belong to Clavien-Dindo grade IIIb. Atelectasis requiring bronchoscopy and empyema belong to Clavien-Dindo grade IIIa. Complications listed as grade II or less are grouped as minor complications. Complications listed as Clavien-Dindo grade III or higher are grouped as major complications. The distribution and rates of each complication are depicted in Table 2.

Mean drainage duration was 5.87±5.3 (range:2-48) days and mean hospital stay was 7.29±5.6 (range:2-48) days.

Definitive histopathological diagnoses of patients are given in Table 3. Seven (3.7%) patients were stage IA1, 43 (23.0%) were IA2, 38 (20.3%) were IA3, 48 (25.7%) were IB, 7 (3.7%) were IIA, 26 (12.7%) were IIB, 15 (7.4%) were IIIA, and 3 (1.6%) were IVA.

RESULTS

I. Preoperative Parameters and Survival

Mean survival of whole group was calculated as 107±4.5 months and 5-year survival was 76.5%. Effects of preoperative parameters on survival are expressed in Table 4.

II. Perioperative Parameters and Survival

We had to convert to thoracotomy in 12 patients due to reasons like hemorrhage and adhesions. Mean survival of patients converted to open surgery was 94±17 months, and mean survival of patients whose operations were completed with VATS was 94±4 months. Their 5-year survival rates are 90.0% and 74.2% respectively. Difference between these groups were not statistically significant (p=0.595). Conversion to open surgery did not have any effect on long term survival as the mean survivals of each group were similar. Among these 12 patients, 1 patient experienced a major complication.

Thirty-four (16.7%) patients underwent segmentectomy and 168 (82.4%) patients underwent lobectomy. For segmentectomies, 5 year survival was 74%, mean survival was 94±9 months and for lebectomies 5 year survival was 76% and mean survival was 106±5 months. Difference was not

Table 4. Preoperative parameters and Survival

Preoperative parameters	5-year survival	p value
Gender		
Male	73.6%	0.103
Female	84.0%	
Age		
≤65	80.6%	0.008
>65	67.7%	
FEV1		
≤80%	66.1%	0.063
>80%	80.1%	
DLCO		
≤80%	51.1%	0.001
>80%	83.2%	

DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: forced expiratory volume in 1 second.

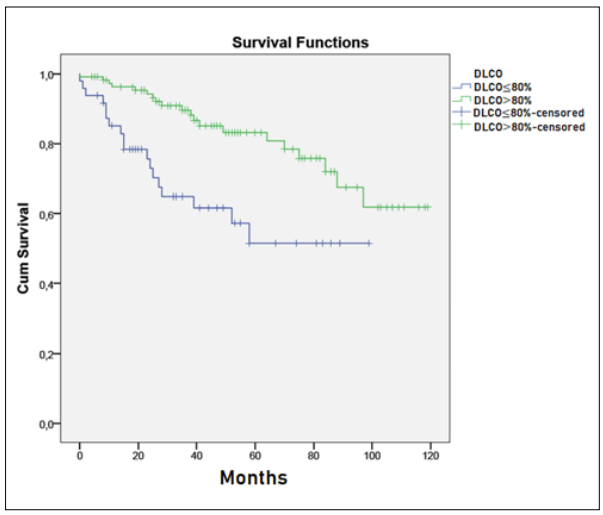

Figure 1. Cumulative survival probability of two groups differentiated by DLCO.

statistically significant (p=0.775) (Figure 1).

III. Postoperative Parameters and Survival

Mortality was observed at 48 patients (23.5%). Postoperative mortality occurred at 4 (2%) patients.

After excluding operative mortalities and comparing patients with or without major or minor complications, it is determined that patients who developed major complications had significantly worse survival (p=0.013). For patients who experienced major complications, 5-year survival was %67.3 and mean survival was 71±10 months, whereas they were 76.2% and 106±4 monthsfor patients discharged without a major complication (p=0.013). Survival of patients who developed minor complications were also studied and similar results were encountered. Five-year survival of these patients were 66.8% and mean survival was 76±5.4 months. On the other hand patients who did not experience any minor complications had a 5 year survival of 79.7% and mean survival of 113±5. This difference was statistically significant (p=0.044).

Mean hospital stay was 7.2±5.6 days. Among whole group, 35.8% was discharged at postoperative day 4 or earlier. Staying only for 4 days or less was related with significantly better survival (86% vs 69%, p=0.017)

DISCUSSION

In this study, we investigated the factors affecting survival for early-stage lung cancer, excluding tumor stage and histopathological subtype. No significant survival difference was observed between the segmentectomy group and the lobectomy group. Segmentectomy, being a parenchymal-sparing surgery compared to lobectomy, is often preferred for patients with small tumors and limited respiratory function.

Our study indicates that a hospital stay of four days or fewer is significantly associated with better survival. The mean length of hospital stay for the patients in our study aligns with those reported in the current literature.[4] However, we are not aware of any studies in the literature reviews that clearly display and compare survival rates based on postoperative hospital stay lengths. Our study provides valuable insights into survival outcomes related to the length of stay.

The length of hospital stay and the occurrence of postoperative complications appear to be interrelated factors. Despite a reduction in postoperative complication rates due to advancements in technology and increased experience with minimally invasive surgery, rates are still around 30%.[5] Pneumonia emerged as the most common postoperative complication in our study. Mei et al. also identified pneumonia as the most common postoperative complication but did not discuss its impact on survival.[6] In line with our findings, Naada et al. observed that the occurrence of postoperative complications is linked to poorer survival outcomes.[7] Wang et al. highlighted that the 5-year survival rate for patients who developed a major complication is 66.6%, while it is 80.9% for those without major complications. They emphasized the statistical significance of this disparity and noted that any postoperative major complication is an indicator of poor prognosis.[8] Contrary to these studies, our research categorizes complications into major and minor, demonstrating that even minor complications adversely affect prognosis, akin to major complications.

Age is a prominent factor influencing survival in lung cancer. Our study indicates that patients aged 65 or younger fare better than their older counterparts, likely due to reduced performance, respiratory capacity, increased tissue fragility, and a propensity for thrombosis.[9,10] Nonetheless, surgical intervention in early-stage lung cancer can yield promising results for patients of advanced age.[11,12]

We observed that diminished preoperative respiratory function correlates with poorer prognosis. Although survival rate differences according to FEV1 values approach but do not achieve statistical significance, these differences are significant when considering DLCO values. Thus, DLCO is considered a more reliable indicator of respiratory function than FEV1. Berry et al. have similarly reported that a low FEV1 value does not significantly impact prognosis,[13] while low DLCO values are associated with a marked difference in outcomes.[14] Galata et al. also found that both preoperative FEV1 and DLCO values significantly influence survival, with DLCO serving as a more predictive measure than FEV1.[15]

With the advancement of technology and surgeons' increasing proficiency with minimally invasive techniques, the scope for such surgeries widens, while contraindications and related complications diminish.[16] Although opinions vary regarding the impact of conversion to open surgery on survival, a definitive consensus remains elusive.[17] A contributing factor to this debate is the enhanced capability to manage complications that may necessitate perioperative conversion, mitigating their impact on sur-

vival outcomes. Hence, a timely and well-executed thoracotomy should not be deemed a failure.[18] Our study demonstrates that patients who underwent conversion did not experience survival rates different from those whose operations were completed thoracoscopically. This is consistent with Park et al., who reported comparable survival and recurrence rates between patients requiring conversion and those managed solely with thoracoscopy.[19] Additionally, Sezen et al. contend that unexpected conversions do not significantly adversely affect long-term survival.[20] Common causes for unanticipated thoracotomy include reduced vascular elasticity due to aging, surgical experience, pleural adhesions, and mediastinal and hilar lymph node metastases.[21]

Limitations

This study presents several limitations. Firstly, the retrospective nature of the study may introduce potential bias. However, it is fortunate that patient records are meticulously maintained. Secondly, the sample size of this study is relatively small. Thirdly, the absence of recurrence-free survival data is another limitation of this study.

Conclusion

This study indicates that age, preoperative DLCO values, the presence of major or minor complications, and the duration of postoperative hospital stays are significant prognostic factors in early-stage lung cancer. Gender, preoperative FEV1 values, conversion to open thoracotomy, and the type of anatomical resection do not appear to significantly impact the prognosis in early-stage lung cancer. Further studies with larger sample sizes are warranted to corroborate the findings reported in this study.

Ethics Committee Approval

This study approved by the Istanbul University Istanbul Medical Faculty Ethics Committee (Date: 10.11.2017, Decision No: 1347).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

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Conflict of Interest

None declared.

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Akciğer Kanserinde Histopatolojik Alt Tip ve Evre Dışında Prognoza Etki Eden Faktörler

Amaç: Akciğer kanserinde sağ kalımı etkileyen temel faktörlerin histopatolojik alt tip ve evre olduğu bilinmektedir. Bu çalışmada torakoskopik anatomik rezeksiyonla tedavi edilen erken evre akciğer kanserinde uzun dönem sonuçları etkileyen faktörleri ortaya çıkarmayı amaçladık.

Gereç ve Yöntem: Çalışma 2006-2018 yılları arasında gerçekleştirildi. Torakoskopik anatomik rezeksiyon uygulanan toplam 204 hasta retrospektif olarak değerlendirildi. Ameliyat öncesi, ameliyat sırası ve ameliyat sonrası parametreler değerlendirilerek sağ kalıma etkileri analiz edildi. Ameliyat öncesi parametreler, yaş, cinsiyet ve solunum fonksiyon testleri – akciğerlerin karbon monoksit (DLCO) kapasitesi idi. Perioperatif parametreler anatomik rezeksiyon tipi ve açık torakotomiye geçiş idi. Ameliyat sonrası parametreler majör ve minör komplikasyonlar, hastanede kalış süresi idi.

Bulgular: Çalışmaya toplam 204 hasta dahil edildi. Hastaların 5 yıllık sağkalımı %76,5 idi. 65 yaşlında veya daha genç olan hataların sağkalımları daha iyi bulundu (%80.6 ve %67.7, p=0.008). DLCO değeri %80'in üzerinde olan hastaların 5 yıllık sağ kalımı %83,2 iken, DLCO değeri %80'e eşit veya daha düşük olan hastaların 5 yıllık sağ kalımı %51,1 olarak tespit edildi (p=0.001). Hastanede 4 gün veya daha az kalış, daha iyi 5 yıllık sağkalım ile ilişkili olduğu görüldü (%86 ve %69, p=0.017).

Sonuç: Çalışmamızda yaş, ameliyat öncesi DLCO değeri, hastanede kalış süresi, ameliyat sonrası komplikasyon gelişiminin sağkalım üzerinde istatistiksel olarak anlamlı olduğu belirlendi. Ancak açık torakotomiye geçiş ve segmentektomi-lobektomi arasındaki farkın sağkalım üzerine spesifik bir etkisi olmadığı görüldü.

Anahtar Sözcükler: Akciğer kanseri; lobektomi; sağkalım.

SCIE DOI: 10.14744/scie.2023.79745
South. Clin. Ist. Euras. 2023;34(4):371-373

Case Report

McLeod Syndrome – A Rare Seen Chorea Etiology with Different Mutations

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Submitted: 02.12.2022
Revised: 14.12.2022
Accepted: 16.07.2023

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Keywords: Chorea; Mcleod syndrome; neuroachantocytosis; novel mutation; point mutation; XK gene.

ABSTRACT

McLeod syndrome is a rare seen chorea etiology. A patient with chorea, epilepsy and cardiac problems usually suggests a neuroachantocytosis syndrome and the definite diagnosis depends on a detailed genetic investigation. Here we report 57 and 39 years old males who developed choreiform movements and tics afterwards, causing social disturbances and walking difficulty. Depending on the acanthocytosis seen on peripheral blood smear and genetic investigation, the patients has been diagnosed as McLeod syndrome with a novel and point mutations.

INTRODUCTION

Neuroacanthocytosis (NA) is a heterogeneous group of hereditary syndromes characterized by the association of neurological abnormalities with acanthocytosis. It consists of a group of genetic diseases associated with the degeneration of the basal ganglia. The prevalence is between one and five in one million for each disease. The rate of acanthocytosis varies among diseases and can be demonstrated by peripheral smear investigations.[1] Acanthocytosis is divided into three groups: Core NA syndrome, NA with lipoprotein disorders, and acanthocytosis in systemic diseases where neurological findings may also be present. Core NA syndromes that are commonly accompanied by movement disorders are chorea-acanthocytosis, X-linked McLeod syndrome (MLS), neurodegeneration with brain iron accumulation, and Huntington disease-like-2 (HDL2). These four syndromes are differentiated from each other depending on clinical and laboratory findings, but the cases are definitely diagnosed depending on genetic investigation.[2] We report two cases of MLS presenting with generalized chorea, tics, and epilepsy.

Case 1

A 57-year-old male consulted us from an epilepsy outpatient clinic with complaints of tic-like kissing movements on the face and involuntary movements in the arms, legs, and tongue. The involuntary movements were diagnosed as chorea. The severity of the choreiform movements was causing an imbalance during walking. All these movements had been present for about 12 years but had increased

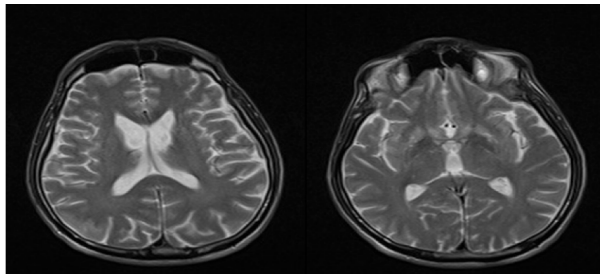

Figure 1. MRI show that putamen and caudat body atrophy.

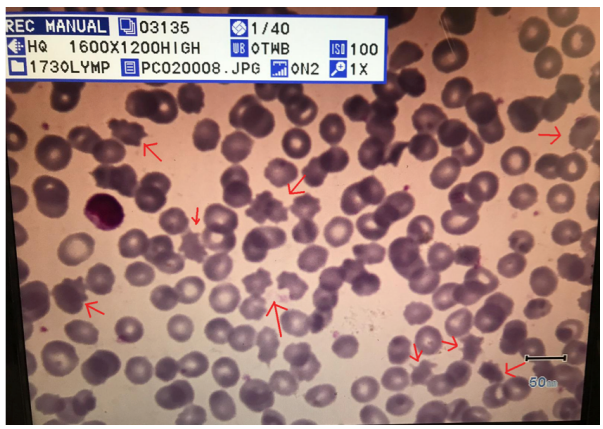

Figure 2. Acanthocytosis in blood smear. Peripheral blood; Wright Stain; ×100 magnification; smear showed frequent acanthocytes.

in the past 5 years. He had a history of epilepsy, which was diagnosed 14 years ago. He was having tonic-clonic generalized seizures, which were under control with levetiracetam treatment. His neurological examination was normal, except for hypoactive deep tendon reflexes and involuntary movements compatible with chorea affecting his face and distal extremities. He had prominent obsessions and anxiety. There was no similar disease history in his family. Laboratory testing was significant for an elevation in a serum creatinine kinase (CK) level of 2148 U/L (normal 62–279). Serum glucose, electrolyte, Vitamin B12, kidney and liver function tests, and the other blood tests were normal. Tumor markers, celiac antibodies, and ELISA antibody were found to be negative. His electroencephalogram (EEG) was normal. An electromyography test was performed, pointing out mild carpal tunnel syndrome and ulnar nerve entrapment on the left side. Magnetic resonance imaging (MRI) of the brain showed atrophy of the basal ganglion and mild generalized brain atrophy (Fig. 1). A peripheral blood smear examination was performed. Acanthocytes were observed in at least 30% of erythrocytes with normochromic normocytic structure (Fig. 2). When evaluated morphologically, the present smear findings were found to be significant for NA. As a result of the laboratory evaluation, a genetic test was sent from the patient with a pre-diagnosis of NA for subgroup examination. Genetic analysis was performed using whole-exome sequencing and bioinformatic analysis method and a novel mutation (p.Leu286TyrfsTer16) (c.854_858delCTCTA) in the XK gene was observed as homozygous in the XK gene, which is compatible with MLS. Since MLS is related to cardiac abnormalities, we referred the patient to a cardiologist. The electrocardiogram and echocardiography were interpreted as normal, but follow-up was recommended for the patient. Tetrabenazine was started for the choreiform movements, and a marked decrease in his choreiform movements was observed.

Case 2

A 39-year-old male patient presented with tic-like kissing movements on the face and involuntary choreiform movements in the arms and legs. In addition, complaints of biting on the lips, the desire to move forward in the tongue, and involuntary noise in the form of throat clearing started. All these movements had been present for about 35 years but had increased in the past 2 years. The patient was diagnosed with chorea in another clinic and tetrabenazine treatment was started. The patient was hospitalized by a psychiatrist due to excessive spending, aggression, depressive mood, obsessions, and suicide attempts 2–3 years before the neurological complaints started, and valproate and clozapine were started with the diagnosis of bipolar affective disorder and obsessive-compulsive disorder. The patient had generalized epileptic seizures 2 years ago. Levetiracetam treatment was started. He also had heart failure and arrhythmia. His older brother had similar involuntary movements in his family history. However, it was reported that he died at the age of fifty. In his neurological examination, there was also dysarthric speech, difficulty swallowing, and tongue protrusion. Extremity distals were atrophic, and hypoactive deep tendon reflexes were present. Laboratory testing was significant for an elevation in a serum CK level of 4536 U/L (normal 62–279). An MRI of the brain showed atrophy of the basal ganglion and mild generalized brain atrophy. In EEG, generalized and frequently recurring sharp-slow wave activity was detected. Sensory-motor axonal neuropathy was detected in nerve conduction study. Acanthocytes were observed in at least 21% of erythrocytes with normochrome normocyte structure. Genetic analysis was performed using the whole-exome sequencing and bioinformatic analysis methods and sequencing analysis of the XK gene: A point mutation of c.397 C>T= (thymine instead of cytosine) mutation was detected in exon 2. The patient was diagnosed with MLS. The tetrabenazine dose was reduced because the patient had a depressive mood. There was no clinical worsening of choreiform movements. 15 IU of botulinum toxin was applied to the genioglossus muscle and 10 IU to the tongue muscle due to swallowing disorders and tongue protrusion. Protrusion was partially reduced.

DISCUSSION

MLS is an X-linked inherited disease associated with poor expression of the blood group antigens Kx and Kell anti-

gens. The onset of neurological symptoms varies between 25 and 60 years.[3] The duration of the illness can usually be more than 30 years. Its clinical features include chorea, facial dyskinesias, and vocalizations. Our patients had facial tic-like kissing movements, which made the case interesting at first sight and also generalized chorea was an evident finding. Tic-like movements are commonly seen in the neurodegenerative diseases HDL and NA.[4] Psychiatric symptoms, including depression, schizophrenia-like psychosis, and obsessive-compulsive disorder, are common in MLS, as seen in our patients.[5] Generalized seizures can be observed in half of the MLS patients. High CK levels are almost always found. Approximately half of the patients develop muscle weakness and atrophy. Cardiomyopathy is seen in 60% of MLS patients. There may be malignant arrhythmia or dilated cardiomyopathy manifested by atrial fibrillation.[1-3] Cardiac complications are common causes of death. Therefore, a cardiologic evaluation should always be performed in MLS patients and asymptomatic carriers of the McLeod blood group. In our cases, facial dyskinesia and tic disorders, anxiety and obsession, and choreiform movements involving extremities, hyporeflexia, and epileptiform seizures mostly suggested chorea-acanthocytosis and MLS. The most important difference between these two syndromes is cardiac involvement which is commonly related to MLS. However, our first patient's cardiac examination did not reveal any pathology; our second patient had dysrhythmia and heart failure. Cardiac abnormalities of MLS patients were examined in a study by Oechslin et al.[6] In this study, one of the patients also did not show any cardiac abnormalities. Neuroradiologically, there is progressive striatal atrophy, especially affecting the head of the caudate nucleus, in MLS patients, as in our patients.[7] Gene deletions, insertions, and point mutations that affect RNA splicing or that lead to premature stop codons have been reported to cause the McLeod phenotype. The McLeod phenotype may also be caused by mutations at a different splice site and by a novel mutation encoding an amino acid substitution that prevents transport to the cell surface. When we investigated the literature, we found that 39 mutations and 17 large-scale deletions had been identified in MLS patients in a review written by Roulis et al.[8]

Conclusion

In our first patient's genetic investigation, a novel mutation has been described after whole-exome analysis. In our second case, a point mutation was detected. While there was no cardiac involvement in the first of our cases, we think that the presence of cardiac involvement in our second case may be due to different mutation types and molecular defects.

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.Ö.B., F.G.Ş.; Design: F.G.Ş., B.E.D.; Supervision: B.Ö.B., F.G.Ş.; Fundings: İ.G.A., A.Ç., F.G.Ş.; Materials: A.Ç., B.E.D.; Data: İ.G.A., A.Ç., F.G.Ş.; Analysis: B.Ö.B., F.G.Ş.; Literature search: F.G.Ş., İ.G.A.; Writing: F.G.Ş., B.E.D.; Critical revision: B.Ö.B., F.G.Ş.

Conflict of Interest

None declared.

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McLeod Sendromu; Farklı Mutasyonlara Sahip Nadir Görülen Bir Kore Nedeni

McLeod sendromu koreye sebep olan nadir görülen bir hastalıktır. Kore, epilepsi ve kardiyak sorunları olan bir hasta genellikle nöroakantositoz sendromunu düşündürür ve kesin tanı ayrıntılı bir genetik incelemeye bağlıdır. Biz burada, daha sonra koreiform hareketler ve tikler geliştiren, yürüme güçlüğü olan ve bu sebeplerle sosyal problemler yaşayan 57 ve 39 yaşındaki erkek hastaları sunuyoruz. Periferik yayma incelemesinde görülen akantositoz ve genetik incelemede tespit edilen yeni ve nokta mutasyon sonucunda hastalara McLeod sendromu tanısı konulmuştur.

Anahtar Sözcükler: Kore, McLeod Sendromu, nokta mutasyon, nöroakantositoz, XK gen, yeni mutasyon.

SCIE DOI: 10.14744/scie.2023.01069
South. Clin. Ist. Euras. 2023;34(4):374-376

Case Report

A Rare Pediatric Tumor of the Posterior Mediastinum: Ganglioneuroblastoma

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Submitted: 18.08.2023
Revised: 18.08.2023
Accepted: 17.11.2023

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Keywords: Childhood tumor; ganglioneuroblastoma; posterior mediastinal tumor.

ABSTRACT

Ganglioneuroblastoma is a rare malignant pediatric tumor located in the posterior mediastinum. A giant mass lesion located in the posterior mediastinum and extending into the spinal canal was observed in a 4-year-old girl admitted to our hospital with walking difficulties. The mass was completely excised with a joint operation of neurosurgery and thoracic surgery. After the operation, the patient regained walking functions.

INTRODUCTION

Neurogenic tumors are the most common mediastinal tumors in children, 20% have a malignant course, and neuroblastomas are the most common malignant neurogenic tumors.[1] Neurogenic tumors of the mediastinum in children and adults may originate from the nerve sheath, sympathetic ganglion, paraganglion cells, and peripheral neuroectodermal tissue.[2] Ganglioneuroblastomas are malignant lesions originating from the sympathic ganglion.

Mediastinal tumors are mostly asymptomatic. However, as the size of the tumor increases, pressure-related symptoms occur. In addition to symptoms such as dyspnea, cough, and chest pain, neurologic symptoms may occur after invasion into the surrounding tissue.[3]

Pathology Neuroblastomas show S-100 expression in immunohistochemical staining, stained with CD34 positive.[4] Ganglioneuroblastomas are rarely seen in the mediastinum and are located mainly in the adrenal glands.[4]

Definitive diagnosis and treatment of the giant tumors of the posterior mediastinum are performed through surgical excision.[3]

CASE REPORT

A 4-year-old girl weighing 18 kg, complaining of numbness in the feet and inability to walk for 3 months, had no known history of disease or medication use. On physical examination, the patient was in good general condition, conscious, and vitals were stable. Respiratory sounds were reduced in the upper right zone, and there was no cyanosis. A decrease in muscle tone in the lower extremities was determined, the motor tone in the upper extremities was normal, and the anal tone could not be assessed.

Posteroanterior chest radiography showed a solid homogeneous opaque mass in the upper zone of the right lung extending from the apex to the sixth intercostal space. Thoracic computed tomography revealed that the mass

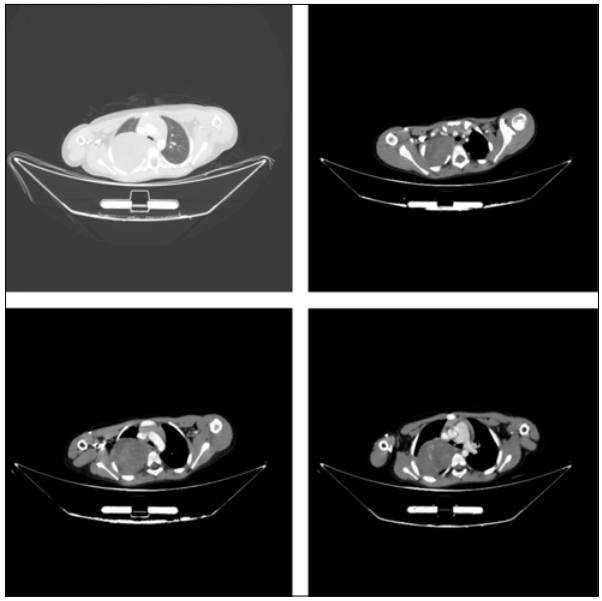

Figure 1. Sections of thorax computerized images of masses located in the posterior mediastinum.

was located in the posterior mediastinum at the C7-T6 level with an approximate size of 7×6.5 (Figure 1). No cranial pathology was observed in the magnetic resonance imaging (MRI), and it was indicated that the mass extended into the spinal canal at the C7-T4 level (Figure 2).

Transthoracic fine-needle aspiration biopsy of the mass was performed by interventional radiology, and the pathology result was reported as stromal cells.

It was decided to operate the patient. In the case coordinated with neurosurgery, C7-T4 hemilaminectomy was performed in the prone position. Then, posterior mediastinal mass excision was performed with lateral thoracotomy in the left lateral decubitus position (Figure 3).

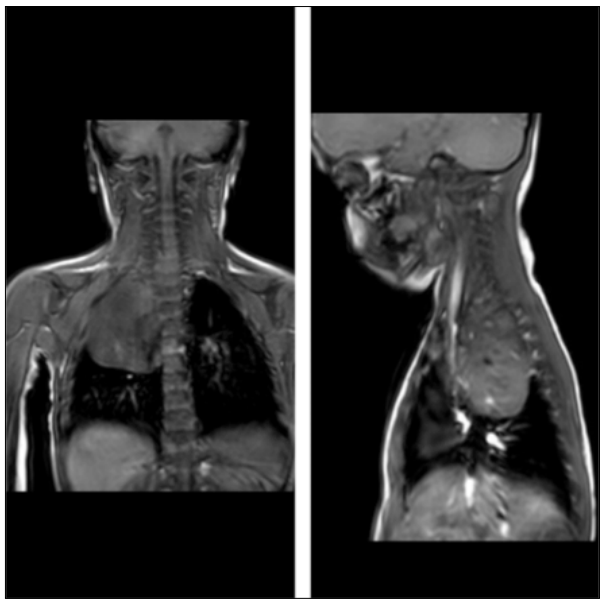

Figure 2. Magnetic resonance imaging sections of the mass located in the posterior mediastinum.

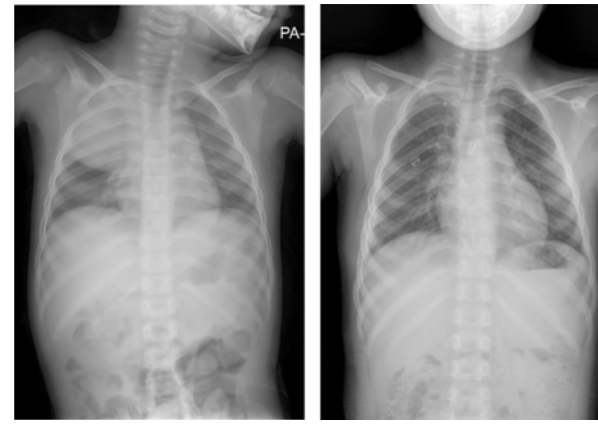

Figure 3. Preoperative and postoperative postero-anterior lung radiographs of the patient.

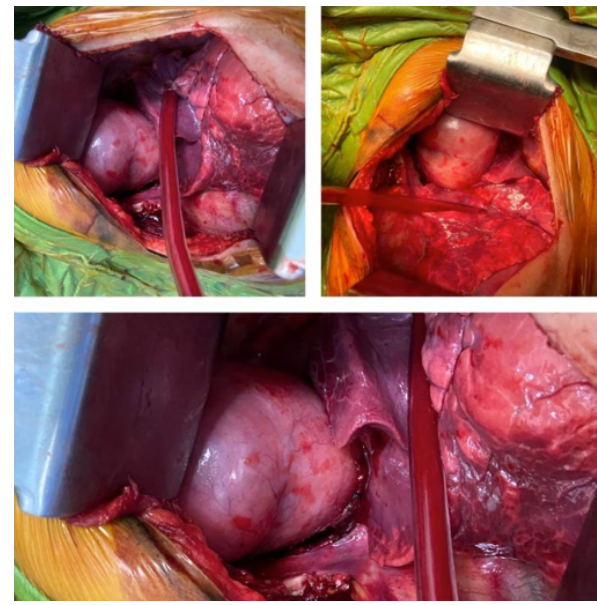

Figure 4. Peroperative photographs of the case.

In the final pathology, the mass size was measured as 8×5×3 cm, and ganglioneuroblastoma diagnosis was applied. CD56, neuronal specific enolase (NSE), S100, and Synaptophysin were found to be positive in the tumor cells.

The patient was discharged with recovery after 6 days in the intensive care unit and 24 days in the clinical ward in the post-operative period. At the 1st-month post-discharge follow-up visit, the patient's gait was ataxic, but motor strength was normal (Figure 4).

DISCUSSION

The mediastinum is divided into three compartments: Anterior, posterior, and middle. Neurogenic tumors constitute 80% of posterior mediastinal tumors.[3] Ganglioneuroblastomas are found in the adrenal gland (35%), retroperitoneum (30%), posterior mediastinum (20%), and pelvis (23%) in order of frequency.[5] Our case is a case of ganglioneuroblastoma located in the posterior mediastinum.

Ganglioneuroblastoma is mainly observed in pediatric patients aged 1 and 2 years, the mean age is 22 months, and it is usually diagnosed at the age of 10 years.[6] Our patient was 4 years old and was diagnosed early according to the general literature.

In imaging methods, they appear as opacities on direct radiography, they are located in the posterior mediastinum in thoracic computed tomography, but the tomography findings are not specific enough.[5] Neuroblastomas and ganglioneuroblastomas contain coarse calcification, while ganglioneuromas contain 20% fine punctate calcification.[7] MRI shows high signal intensity on T1-weighted imaging and low signal intensity on T2-weighted imaging and evaluates invasion better.[5] In the computed tomography scans, our case did not show any calcification. In the MRI, extension into the spinal canal was observed.

Our patient underwent pre-operative transthoracic fine needle aspiration biopsy but could not be diagnosed. Histopathologic diagnosis is not mandatory for a surgical decision.[3] Chemotherapy and radiotherapy are among the treatment options in cases where surgical treatment is not possible.[5]

Diagnostic markers of ganglioneuroblastomas include catecholamines, valinmandalic acid, and homovalenic acid.[8] Biochemistry markers were not studied in our patient because the operation was scheduled in the early period.

In a reported case, a 4-year-old pediatric patient underwent an operation due to a mass located in the posterior mediastinum causing a cervical intradural extension, and the patient regained upper and lower extremity strength after the operation.[9] In another case report of ganglioneuroblastoma in an 8-month-old child, the patient regained muscle strength in the feet with laminectomy and excision.[10] In our case, lower extremity motor power was fully restored with successful surgery.

The final pathology of our case was reported as nodular-type ganglioneuroblastoma (Schwannian stroma-rich/dominant and Schwannian stroma-poor). The International Neuroblastoma Pathology Classification based on the Shimada system is used in the classification of neuroblastomas.[11] In neuroblastomas, synaptophysin, chromogranin, CD56, NSE, and protein gene product 9.5 (PGP9.5) are stained positive, although not specific for diagnosis.[11] In our case, CD56, chromogranin, NSE, S100, synaptophysin are stained positive.

Conclusion

Our case report is presented to draw attention to rare pediatric neurological tumors. We believe that successful surgery in mediastinal neurological tumors of pediatric patients performed by experienced centers would yield satisfactory results.

Peer-review

Externally peer-reviewed.

Authorship Contributions

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Conflict of Interest

None declared.

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Posterior Mediastenin Nadir Görülen Çocukluk Çağı Tümörü: Ganglionöroblastoma

Ganglionöroblastoma, posterior mediastende yerleşimli çocukluk döneminin nadir görülen malign bir tümörüdür. Yürüme güçlüğü ile hastanemize başvuran 4 yaşındaki kız çocuğunda posterior mediasten yerleşimli spinal kanal içine uzanan dev kitle lezyon izlendi. Beyin cerrahisi ve göğüs cerrahisini ortak operasyonu ile kitle total eksize edildi. Ameliyat sonrası hasta yürüme fonksiyonlarını tekrar kazandı.

Anahtar Sözcükler: Çocukluk çağı tümörü; ganglionöroblastoma; posterior mediasten tümörü.

SCIE DOI: 10.14744/scie.2023.93585
South. Clin. Ist. Euras. 2023;34(4):377-379

Case Report

A Rare Case of Severe Metabolic Acidosis Caused by Toluene Abuse

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Submitted: 04.08.2023
Revised: 27.11.2023
Accepted: 04.12.2023

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Keywords: Emergency department; metabolic acidosis; poisoning; Toluene.

ABSTRACT

Toluene is a solvent used in various industries as a raw material to produce organic compounds and in the manufacture of diverse products. Contact with toluene can occur both accidentally and intentionally. Intoxication with toluene and its by-products, whether intentional or accidental, can be toxic to all systems, with the cardio-pulmonary system being primarily affected. The intentional use of toluene leads to psychoactive effects, including euphoria, which makes it the most widely inhaled volatile drug among all age groups in many countries. Renal tubular acidosis is the most common complication arising from toluene intoxication. This case report will discuss a 38-year-old patient who was admitted to the emergency service of our hospital.

INTRODUCTION

Toluene is widely utilized as a raw material in the production of organic compounds, such as benzene, across various industrial sectors. These compounds are extensively applied in different industries and used in products like gasoline, spray paint, cleaning agents, and paint thinners. However, direct inhalation exposure to toluene can result in environmental, accidental, and intentional intoxications. Firstly, its easy accessibility and relatively low cost make it a common choice compared to other inhalants of abuse. Secondly, it can be inhaled either in its pure form or as a component of numerous commercial products. Thirdly, it induces acute psychoactive and neurological effects, such as euphoria, positioning toluene as the most commonly abused inhalant across all age groups in many countries.[1,2] Toluene inhalation is associated with various pathologies, including severe metabolic changes like renal tubular acidosis type 1 (RTA-1). Additionally, toluene can cause severe arrhythmias, including tachyarrhythmia and bradyarrhythmia. ST wave pattern alterations, indicative of hypokalemia and acute myocardial infarction, have been documented in cases of toluene intoxication. Rhabdomyolysis and acute hepatorenal injuries have also been reported. Consequently, toluene exposure may constitute a risk factor for adverse outcomes.[1] Toluene is metabolized into benzoic acid, which the kidneys then eliminate.[3] Distal RTA-1 is traditionally characterized as hyperchloremic with a normal anion gap, accompanied by hypokalemia and muscle paralysis, indicative of toluene intoxication.[4] This case report will discuss a 38-year-old man who was found in an unconscious state due to toluene poisoning.

CASE REPORT

A 38-year-old male patient with a history of toluene abuse

was brought to our emergency room (ER) in an unconscious state. His relatives reported that his symptoms rapidly worsened minutes after they found him sniffing paint thinners in his room, following which he collapsed. They also noted that he had not taken any medications or other substances. Upon arrival at our ER, he had a Glasgow Coma Scale score of 3, with bilateral dilated pupils unresponsive to direct and indirect light. His vital signs were a blood pressure of 70/50 mmHg, a pulse of 52 beats/min, and an oxygen saturation rate of 55%. Nasal oxygen was administered at 2L/min due to the low saturation rate. An ECG showed sinus bradycardia, and vascular access was established in both arms. A complete blood count (CBC), serum biochemistry, and a toxicology panel were conducted. Given the family's statement and the patient's bradycardia and bradypnea, Naloxone at 0.4mg/mL and intravenous fluids were administered. A follow-up showed a pulse of 25 beats/min, prompting the administration of 0.5mg/mL atropine. Initial laboratory results indicated: sodium at 144 mmol/L; potassium at 5.1 mmol/L; chloride at 100 mmol/L; glucose at 309mg/dL; creatinine at 1.38mg/dL. A venous blood gas analysis revealed a pH of 6.400 (7.35-7.45), a pCO2 of 81.8 mmHg, a pO2 of 63.1 mmHg (83-108), bicarbonate at 4.7 mmHg (22.5-26.9), and lactate at 24 mmol/L (0.5-1.6) - indicative of severe metabolic acidosis. Approximately five minutes later, the patient had no palpable carotid or femoral pulse and no spontaneous respiration. Resuscitation efforts were initiated, and rapid sequence intubation was performed. After 10 minutes, a palpable pulse returned along with spontaneous respirations. The patient received 40 mcg/min of inotropic support, 15 mcg/min of dopamine, and 100 mEq of bicarbonate. Post-treatment, the patient's vitals were a blood pressure of 100/50mmHg, oxygen saturation at 99% (while intubated), and a pulse of 90 beats/min. A follow-up venous blood gas showed a slight increase in pH to 6.467 (7.35-7.45). A CT scan under a physician's supervision revealed no pathological findings. The patient was evaluated in the ER by anesthesiologists, and admission to the intensive care unit (ICU) was recommended. The toxicology panel, which was tested on a urine sample, did not detect amphetamines, benzodiazepines, buprenorphine, cannabinoids, cocaine, ecstasy, heroin metabolites, or opioids. The patient was stabilized in the ER and transferred to a hospital with a specialized medical toxicology ICU. The patient remained intubated in the ICU for twenty days; however, he succumbed to his condition twenty days after ICU admission.

DISCUSSION

Death related to aliphatic and aromatic hydrocarbon intoxication most commonly results from asphyxia. Guo described a phenomenon known as "sudden sniffing death," which refers to cardiovascular collapse following the deliberate inhalation of aliphatic and aromatic hydrocarbons within a few hours of exposure. While the abuse of toluene is globally widespread, instances of sudden sniffing death are rare.[5] Toluene rapidly diffuses into the bloodstream and penetrates lipid-rich tissues. It is oxidized in tissues, leading to the formation of lipid peroxidation products and free radicals.[3] The metabolism of toluene by cytochrome P-450 results in benzoic and hippuric acids, which are excreted by the kidneys and detectable in urine.[1,3] Exposure to toluene can also lead to electrolyte imbalances and acid-base disturbances. It is reported that metabolic acidosis occurs in 87% of toluene intoxication cases, indicative of distal tubular acidosis.[6] In the present case, the initial venous blood gas showed a pH of 6.400 (7.35-7.45), signifying severe metabolic acidosis. Toluene sniffing can also induce normal anion gap acidosis by hindering renal elimination of ammonium ions, the primary carrier for excess hydrogen ions.[7] Hokenek et al.[8] analyzed 274 patients in intensive care and found that lactate levels of 4.64±4.696 mmol/L are associated with early mortality. In this case, the lactate level was alarmingly high at 24.0 mmol/L (0.5-1.6). Moreover, toluene intoxication can impact the lungs, heart, liver, kidneys, and central nervous system. Cardiac involvement is one of the primary consequences of toluene intoxication, with tachyarrhythmia being the generally expected clinical presentation. However, there have been reports that toluene can also induce bradyarrhythmia, heart block, and AV dissociation.[9] In this case, sinus bradycardia was observed.

Conclusion

In managing patients exposed to toxic levels of toluene, it is critical to recognize that they may present with severe metabolic acidosis and elevated lactate levels, which are associated with an increased risk of mortality. Moreover, cardiac complications can manifest not only as severe tachyarrhythmia but also as bradyarrhythmia, heart block, and AV dissociation. It is essential to acknowledge that intentional toluene inhalation poses a significant public health issue and presents a considerable challenge in emergency medicine due to its potential to cause sudden death through severe metabolic and cardiopulmonary outcomes.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: C.A.T.; Design: A.U.S.; Supervision: O.G.; Fundings: D.Ö.; Materials: C.A.T.; Data: A.U.S.; Analysis: O.G.; Literature search: O.G.; Writing: O.G.; Critical revision: C.A.T.

Conflict of Interest

None declared.

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Toluen Kullanımının Neden Olduğu Derin Metabolik Asidoz Vakası

Amaç: Toluen, birçok endüstride organik bileşikler üretmek için hammadde olarak kullanılan ve çeşitli ürünlerin yapımında kullanılan bir çözücüdür. Toluen ile temasa geçmek hem kazara hem de kasıtlı olabilir. Toluen ve yan ürünleri ile hem kasıtlı hem de kazara zehirlenme, başta kardiyopulmoner sistem olmak üzere tüm sistemlerde toksik olabilir. Toluenin kasıtlı kullanımı, öfori de dahil olmak üzere psikoaktif sonuçlara neden olur ve bu da onu birçok ülkede her yaştan insan arasında en yaygın olarak solunan uçucu ilaç haline getirir. Toluen zehirlenmesinin en yaygın komplikasyonu renal tübüler asidozdur. Bu durumda hastanemiz acil servisine başvuran 38 yaşındaki hastanın raporu tartışılacaktır.

Anahtar Sözcükler: Acil departmanı; metabolik asidoz; toluen; zehirlenme.