e-ISSN: 2687-4717

7 cilt volume
1 sayı issue
2025 şubat february

HİTİT MEDICAL JOURNAL

HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

HİTİT ÜNİVERSİTESİ YAYINLARI

HMJ

HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025
Periyot: Yılda 3 Sayı (Şubat & Haziran & Ekim) | Period: 3 Issues per Year (February & June & October)

YAYIN DİLİ | LANGUAGE OF PUBLICATION

Türkçe & İngilizce | Turkish & English

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YAYINCI | PUBLISHER

Hitit Üniversitesi Yayınları | Hitit University Press

HAKEM KURULU | REFEREE BOARD

Hitit Medical Journal Dergisi, çift taraflı kör hakemlik sistemi kullanmaktadır. Hakem isimleri gizli tutulmakta ve yayımlanmamaktadır.

Hitit Medical Journal uses a double-blind review. Referee names are kept strictly confidential.

LOCKSS: https://dergipark.org.tr/tr/pub/hititmedj/lockss-manifest

OAI: https://dergipark.org.tr/api/public/oai/hititmedj/

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Hitit Medical Journal'ın yeni sayısıyla sizlerle buluşmanın gururunu ve heyecanını yaşıyoruz. Dergimiz, bilimsel niteliği ve yayın ilkelerine olan bağlılığı sayesinde her geçen gün büyüyerek ulusal ve uluslararası akademik camiada daha fazla tanınır hale gelmektedir. Artan ilgi, bizlere büyük bir motivasyon kaynağı olmakla birlikte, akademik sorumluluğumuzun da artmasına vesile olmaktadır.

Bu sayıda, dergimize olan ilginin giderek arttığını bir kez daha gözlemliyoruz. Bilimsel çalışmaların paylaşılması ve akademik bilginin yayınlanmasına verdiğimiz önem doğrultusunda, makale değerlendirme süreçlerini titizlikle ve şeffaf bir şekilde yürütmeye devam ediyoruz. Amacımız, nitelikli bilimsel çalışmaları en kısa sürede siz değerli okuyucularımızla buluşturarak bilim dünyasına katkı sağlamaktır.

Bu sayımızda, tıp alanının farklı uzmanlık alanlarından ve disiplinlerinden toplam 20 makaleyi sizlere sunmaktan mutluluk duyuyoruz. Bunlar 13 orijinal araştırma makalesi, 3 derleme, 2 olgu sunumu ve 2 editöre mektup olup, literatüre önemli katkılar sunacak niteliktedir. Her bir çalışmanın bilimsel gelişime ışık tutmasını ve sağlık alanında yeni bakış açıları kazandırmasını diliyoruz.

Hitit Medical Journal olarak bizlere güvenen, bilimsel birikimlerini bizimle paylaşan tüm yazarlarımıza ve ilgileriyle bizleri motive eden siz değerli okuyucularımıza en içten teşekkürlerimizi sunarız. Bilimin ışığında hep birlikte ilerlemek dileğiyle, keyifli ve ilham verici bir okuma deneyimi dileriz.

Doç. Dr. Abdulkerim YILDIZ
HMJ Editöryal Kurul adına

From the Editor

Dear Scientists and Esteemed Readers,

We are proud and excited to meet you with the new issue of Hitit Medical Journal. Our journal is growing day by day thanks to its scientific quality and commitment to publication principles and is becoming more recognized in the national and international academic community. The increasing interest is a great source of motivation for us and also increases our academic responsibility.

In this issue, we observe once again that the interest in our journal is increasing. In line with the importance, we attach to sharing scientific studies and publishing academic knowledge, we continue to carry out article evaluation processes meticulously and transparently. Our aim is to contribute to the world of science by bringing qualified scientific studies together with you, our valued readers, as soon as possible.

In this issue, we are happy to present to you a total of 20 articles from different areas of expertise and disciplines in the field of medicine. These are 13 original research articles, 3 reviews, 2 case reports and 2 letters to the editor, and they are of a nature that will make significant contributions to the literature. We hope that each study will shed light on scientific development and provide new perspectives in the field of health.

As Hitit Medical Journal, we would like to express our sincere gratitude to all our authors who trust us and share their scientific knowledge with us, and to our valued readers who motivate us with their interest. We wish you an enjoyable and inspiring reading experience, wishing to progress together in the light of science.

Doç. Dr. Abdulkerim YILDIZ
On behalf of the HMJ Editorial Board

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ŞUBAT - 2025
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ELEKTRONİK DERGİ
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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Comparison of Extracorporeal Shock Wave Therapy, Ultrasound and Dexamethasone Iontophoresis in Patients with Lateral Epicondylitis

Lateral Epikondilitli Hastalarda Ekstrakorporeal Şok Dalga Tedavisi, Ultrason ve Deksametazon İyontoforezinin Karşılaştırılması

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1462592
Geliş Tarihi | Received: 01.04.2024
Kabul Tarihi | Accepted: 25.09.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Başaran PÖ, Doğan AG. Comparison of extracorporeal shock wave therapy, ultrasound and dexamethasone iontophoresis in patients with lateral epicondylitis. Hitit Medical Journal 2025;7(1):1-9. https://doi.org/10.52827/hititmedj.1462592

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 14/06/2023 tarihinde Hitit Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2023-77.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: PÖB, AGD Tasarım: PÖB, AGD Veri Toplama/Veri İşleme: PÖB, AGD Veri Analizi: PÖB, AGD Makalenin Hazırlanması: PÖB, AGD.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Hitit University Clinical Research Ethics Committee on 14/06/2023. Decision no:2023-77.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: PÖB, AGD Design: PÖB, AGD Data Collection/Data Processing: PÖB, AGD Data Analysis: PÖB, AGD Manuscript Preparation: PÖB, AGD.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Comparison of Extracorporeal Shock Wave Therapy, Ultrasound and Dexamethasone Iontophoresis in Patients with Lateral Epicondylitis

ABSTRACT

Objective: The purpose of this study is to determine the effectiveness of extracorporeal shock wave therapy (ESWT), ultrasound (US), and dexamethasone iontophoresis treatments on pain, grip strength, functionality, and quality of life in patients with lateral epicondylitis, and overdetermine the superiority of the treatments to each other.

Material and Method: This single-blind, prospective study included 78 patients who were diagnosed with lateral epicondylitis. The patients were randomized into three groups. The same physiotherapy program consisted of hot packs, transcutaneous electrical nerve stimulation (TENS), and exercises were administered to all groups. All exercises were performed under the supervision of a qualified physiotherapist. In addition to a 10-day physiotherapy program, every 5 days, a total 3 sessions of ESWT were conducted to the 1st group, 10 days of US applied to the 2nd group, and 10 days of dexamethasone iontophoresis therapy to the 3rd group. Evaluations were carried out before, and 1 month after treatment. Pain severity levels were measured using the numeric rating scale (NRS), disability using the Quick Disabilities of the Arm, Shoulder, and Hand (Quick DASH), quality of life using the Nottingham Health Profile (NHP), and grip strength using a dynamometer and pinch strength using a pinch meter.

Results: The groups were similar in demographic and clinical characteristics. A significant temporal change was found in three groups in terms of pain severity, disability, grip strength, and quality of life at the first month after treatment. When the efficacy of these treatments was compared after treatment in the first month, dexamethasone iontophoresis was statistically superior to US, and ESWT in terms of pain, and quality of life ($p<0.001$, $p=0.007$, $p<0.001$, $p<0.001$ respectively). Also, the US was superior to ESWT in terms of quality of life ($p<0.001$).

Conclusion: Dexamethasone iontophoresis is more effective in functional and clinical improvement in the treatment of patients with lateral epicondylitis.

Keywords: Lateral epicondylitis, ultrasound, dexamethasone iontophoresis, extracorporeal shock wave therapy, tennis elbow

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ÖZET

Amaç: Bu çalışmanın amacı, lateral epikondilitli hastalarda ekstrakorporeal şok dalga tedavisi (ESWT), ultrason (US) ve deksametazon iyontoforez tedavilerinin ağrı, kavrama gücü, fonksiyonellik ve yaşam kalitesi üzerindeki etkinliğini belirlemek ve hangi tedavinin daha etkili olabileceğini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu tek kör, prospektif, randomize çalışmaya lateral epikondilit tanısı konan 78 hasta dahil edildi. Hastalar üç gruba randomize edildi. Bu tek kör, prospektif, randomize çalışmaya lateral epikondilit tanısı konan 78 hasta dahil edildi. Hastalar üç gruba randomize edildi. Tüm gruplar sıcak paketler, transkütanöz elektriksel sinir stimülasyonu (TENS) ve gözetimli egzersizleri içeren bir fizyoterapi programı uygulandı. Tüm egzersizler deneyimli bir fizyoterapist gözetiminde gerçekleştirildi. 10 günlük fizyoterapi programına ek olarak, 1. gruba her 5 günde bir toplam 3 seans ESWT, 2. gruba 10 gün US ve 3. gruba 10 gün deksametazon iyontoforez tedavisi uygulandı. Değerlendirmeler tedaviden önce ve 1 ayın sonunda yapıldı. Ağrı şiddeti sayısal derecelendirme ölçeği (NRS) ile, özürlülük kol, omuz ve el hızlı özürlülük ölçeği (Quick DASH) ile, yaşam kalitesi Nottingham Sağlık Profili (NHP) ile, kavrama gücü dinamometre ile ve parmak gücü pinchmetre ile ölçüldü.

Bulgular: Gruplar demografik ve klinik özellikler açısından benzerdi. Tedaviden sonraki ilk ayda ağrı şiddeti, özürlülük, kavrama gücü ve yaşam kalitesi açısından üç grupta da anlamlı iyileşme saptandı. Tedavi sonrası birinci ayda bu tedavilerin etkinliği karşılaştırıldığında, deksametazon iyontoforez, ağrı, özürlülük ve yaşam kalitesi açısından US ve ESWT'den istatistiksel olarak üstün olarak saptandı (sırasıyla, $p<0.001$, $p=0.007$, $p<0.001$, $p<0.001$). Ayrıca, US yaşam kalitesi açısından ESWT'den daha üstün olarak saptandı ($p<0.001$).

Sonuç: Deksametazon iyontoforezi lateral epikondilitli hastaların tedavisinde fonksiyonel ve klinik iyileşmede daha etkilidir.

Anahtar Sözcükler: Deksametazon iyontoforezi, ekstrakorporeal şok dalga tedavisi, lateral epikondilit, tenisçi dirseği, ultrason

Introduction

Lateral epicondylitis (LE) is one of the most common causes of nontraumatic elbow pain, which develops as a result of repetitive stresses due to overuse of the forearm muscles and is also called tennis elbow (1,2). It has a prevalence ranging from 1-3% in the general population, and the age of onset is generally between 35 and 55 years. It is seen in women, and more frequently on the dominant hand side (3). Typical symptom duration is between 6 and 24 months (4). Previously, lateral epicondylitis was thought to be an inflammatory process, but in some studies, inflammatory cells were not found in histopathological samples, and it was seen as a tendinosis condition that develops as a result of angiofibroblastic degeneration of the forearm extensor muscles (5). Excessive stress on the insertion of the extensor carpi radialis brevis and other extensor muscles is the primary cause of the pathology (6). The main objectives in the treatment of lateral epicondylitis after diagnosis are; relief of pain, accelerating the healing process, reduction of overloading on the elbow joint, and return of the patient to daily life activities (7).

Although conservative, and surgical treatments can be used in the treatment, conservative treatments offer improvement in 95% of the cases. On the other hand, due to the uncertainty about the etiology of lateral epicondylitis, and the pathophysiology of the disease that is not precisely known, no treatment method that can be accepted as the gold standard has not been found (8). Conservative treatment options include rest, patient education, behavior modification, non-steroidal anti-inflammatory drugs, use of splints, ice application, electrotherapy, massage, manual therapy, stretching, and strengthening exercises, extracorporeal shock wave therapy (ESWT), dry needling, balneotherapy, cryotherapy, steroid injections, hyaluronic acid injections, plasma rich platelet injections, and prolotherapy applications (9).

Theuropatic Ultrasound (US) is a conservative treatment method for lateral epicondylitis. By the help of US waves that penetrate to the muscles, blood flow increases in the tissue, the inflammatory mediators that lead to pain and muscle spasms are removed from the tissue and the healing process begins (10).

Another noninvasive method is ESWT. ESWT is commonly used in musculoskeletal pathologies (11). In the ESWT high high-intensity acoustic pressure waves are applied to the tissue within a short period of time. Studies have shown that with the help of ESWT collagen synthesis increases in soft tissues, and tendons, and vascularization accelerates in the tissue also reduces pain (12).

Iontophoresis is another conservative treatment. In iontophoresis, ionized substances are transferred through the skin to the tissues with electrical polarization. Thus, dexamethasone iontophoresis can provide an anti-inflammatory effect without reaching systemic concentrations in the blood (13). By the way, the treatment of lateral epicondylitis without steroid injections may be successful with the help of dexamethasone iontophoresis.

The purpose of our study; is to evaluate the efficacy of ESWT, US, and iontophoresis treatments in terms of pain, grip strength, functionality, and quality of life in patients with lateral epicondylitis and to determine the superiority of the treatments against each other.

Patients and Methods

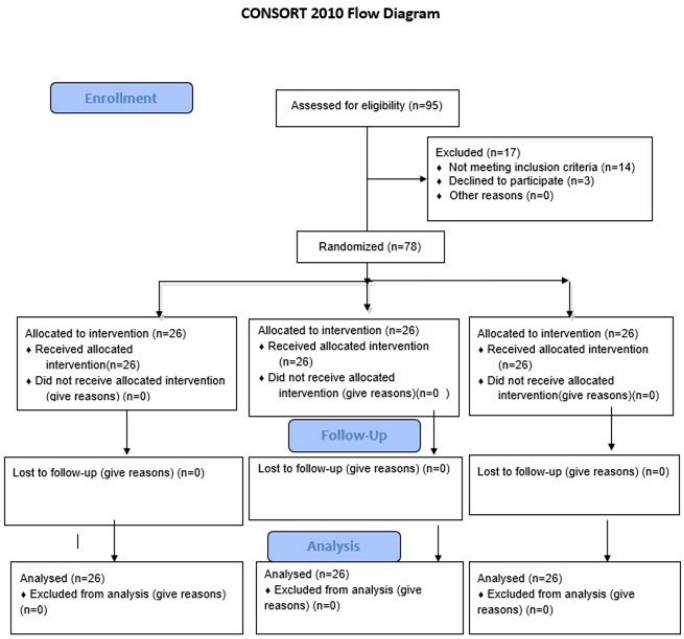
Study Design and Patients

This is a prospective randomized single-blind clinical study. A total of 78 patients aged between 18-65 who were diagnosed with lateral epicondylitis between June 2023 and January 2024 were included in our study. The study was approved by the Hitit University Ethics Committee (14.06.2023 number 2023-77) and written informed consent was obtained from all the patients. The study was carried out in accordance with the principles of the Declaration of Helsinki. The protocol was registered at clinical trials (registration number NCT06189521).

Patients who had chronic pain in the lateral epicondyle for at least four weeks, detection of sensitivity by palpation on the lateral epicondyle, and having positivity in at least two special tests (Cozen test, Maudsley test, and Mills test) were included in the study. Patients with acute pain were not included in the study. Physical therapy, ESWT, or local injections for lateral epicondylitis in the last 3 months, the presence of cervical radiculopathy, carpal tunnel syndrome, other neuropathic diseases,

neurologic diseases, medial epicondylitis, systemic inflammatory diseases, tenderness or swelling at the ipsilateral extremity and fibromyalgia have been excluded. The patients were randomized into three groups by a physiotherapist with sealed envelopes. Clinicians who evaluate patients before and after treatment (specialist physicians P.Ö.B and A.G.D) were blinded to the patient groups. The flow diagram of the patients is shown in Figure I.

Figure 1. Flow Diagram



Treatment Applications

The same physiotherapy program was applied to all groups. The physiotherapy program consisted of hot packs and transcutaneous electrical nerve stimulation (TENS) for 10 minutes and stretching and eccentric strengthening exercises were given to all groups. All exercises were performed under the supervision of the same physiotherapist. Only stretching exercises were performed in the first week and strengthening exercises were added to these exercises in the second week. All patients tolerated the exercises and no patient discontinued the treatment. Paracetamol tablets are prescribed to patients in need due to pain. Paracetamol was prescribed to 6 patients in the ESWT group, 9 patients in the US group, and 7 patients in the control group. Patients were not given splints for LE.

In addition to the 10-day of physiotherapy program, in the first group every 5 days, a total of 3 sessions of ESWT were applied at 1.8 bar, 10.0 Hz, 2000 beats (Elmed Vibrolith Ortho, ESWT-RSWT, Elmed medical systems, USA).

In the second group, 10 days of US were applied at 1.5 watt/cm^2, 1mHz frequency continuous mode to the painful area for 5 minutes, 5 days a week for two weeks (Chattanooga Intelect Advanced Monochromatic Combo 2772, Chattanooga Group, USA).

In the third group, 10 days of dexamethasone iontophoresis therapy were applied. 10 days for 10 minutes. 0,1% dexamethasone ophthalmic pomade was applied to the anodal electrode and placed on the lateral epicondyle and 0.1-0.2 mA/cm^2 galvanic current was applied in each session (ES-522; 2 channel low and medium frequency Electrotherapy, ITO Co. Ltd., Tokyo, Japan).

Clinical Assessments

The clinical and demographic data of the patients were recorded. Numerical rating scale (NRS) was used for the pain assessment. Patients rated their pain from 0 no pain to 10 worst pain (14).

The hand grip strength (Hgs) was measured with a Jamar hydraulic hand dynamometer (Saehan, SH5001) in kilograms. Measurements were done while the patients were sitting in a chair in two positions. In the first position, the patients' elbows were fully extended (Hgs ext), in the second position the patient's elbows were 90 degrees flexed (Hgs flex) without touching the chair. Measurements were made with the affected extremity. The tests were repeated three times with a 30-second rest between them and a mean score was calculated (15).

The strength of the pinch was measured using a hydraulic pinch gauge (Saehan, SH5005) with two points and three points with both hands. At the two points; pinch gauge was placed between the thumb and the lateral part of the second finger. In the three points; the pinch gauge was placed between the second and third finger upside and the thumb downside (16).

Upper extremity disability levels were assessed with the Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire. QuickDASH is composed of 11 questions to evaluate daily living activities. Each question is scored from 1 to 5. Higher scores indicate a poorer level of function. The Turkish

version of the test was evaluated (17).

Quality of life was measured by Nottingham Health Profile (NHP). The NHP is made up of 6 subgroups including pain, energy, sleep, social isolation, physical activity, and emotional reactions. The test was composed of 38 questions and the total score ranged from zero to 100 (18).

Statistical Analyses

In the study power analysis performed by examining reference studies in the literature and the sample size to obtain a significant result, the total number of samples was calculated with the parameters effect size =0.79, α error probability =0.05, power (1-β error probability) =0.80 was calculated as totally 76 patients (G-Power v3.1.9.7) (5). Data were analyzed using the statistical package program IBM SPSS Statistics Standard Concurrent User V 29 (IBM Corp., Armonk, New York, USA). Descriptive statistics were given as number of units (n), percentage (%), mean ± standard deviation, median, minimum, maximum, and inter-cartillary distance values. The normal distribution of the numerical variables was evaluated by the Shapiro Wilk normality test. The homogeneity of variances was evaluated by Levene's test. Age, gender, and side variables were compared by one-way analysis of variance and Pearson chi-square analysis. Pre-treatment and treatment numerical variables were compared by groups with repeated measures of two-way analysis of variance if the assumptions were met. Bonferroni correction was applied in all pairwise comparisons. If the assumptions were not met, intergroup comparisons for numerical variables were made by Kruskal-Wallis analysis, and intragroup comparisons were made by Wilcoxon test. The dunn-Bonferroni correction was applied for pairwise comparisons in the Kruskal-Wallis analysis. p<0.05 was considered statistically significant

Results

A total of 78 LE patients were included in the study. Groups are similar in terms of age, sex, and hand dominancy as seen in Table I. No side effects were observed in patients during treatment. In all treatment groups, ESWT, US, and iontophoresis there was a significant decrease in NRS (*p<0.001*) and Quick DASH values (*p<0.001*) between pre-treatment and after treatment one-month follow-up controls. A significant increase was found in the hand grip strength in both elbows 90 degrees flexed (*p<0.001, p=0.013, p<0.001*, respectively) and fully extended (*p=0.001*), and all NHP subgroups at one-month follow-up compared to pre-treatment in all groups. A significant increase was found in two-point and three-point pinch values before and after one-month follow-up in ESWT and iontophoresis groups but not in the US group (Table II).

Table I. Demographic and Clinical Characteristics of the Treatment Groups

	ESWT *n*=26	**Ultrasound** *n*=26	**Iontophoresis** *n*=26	*p*
Age, (*year*)	44.6±7.8 27-59	44.9±7.9 26-63	47.6±5.9 37-60	0.295Φ
Sex, *n* (%)				
Male	**13 (50.0)**	**12 (46.2)**	**15 (57.7)**	**0.698Φ**
Female	**13 (50.0)**	**14 (53.8)**	**11 (42.3)**	
Elbow pain duration (months)	4 (1-9)	5 (1-9)	6 (3-8)	0.067‡
Affected side, *n* (%)				
Left	**11 (42.3)**	**13 (50.0)**	**9 (34.6)**	**0.532Φ**
Right	**15 (57.7)**	**13 (50.0)**	**17 (65.4)**	
Hand Dominancy				
Right	**24 (92.3)**	**24 (92.3)**	**25(96.2)**	**0.635Φ**
Left	**2 (7.7)**	**2 (7.7)**	**1(3.8)**	

n: Number of patients, %: Percentage of columns, age summarized as mean±standard deviation (min-max), pain duration summarized as median (min-max). Φ: One-way analysis of variance, ‡: Kruskal-Wallis analysis, Φ: Pearson chi-square analysis

When the groups were compared with each other, the decrease in NRS levels and Quick DASH values at one-month follow-up was significantly higher in the iontophoresis group than in the ESWT and US group (*p<0.001, p<0.001*), The decrease in NRS values levels and Quick DASH values in ESWT and US groups was not statistically different (*p=0.999*, *p=0.719*, respectively).

The changes in Hgs flex values before and after treatment were statistically different between the groups (*p<0.001*). The increase in Hgs flex values in the iontophoresis group was statistically higher than in the ESWT and US groups (*p=0.001; p=0.038*). The increase in Hgs flex values was not statistically different in the ESWT and US groups (*p=0.607*). The changes in Hgs ext values before and after treatment were statistically different between the

Table II. Comparison of Variables According to Groups

	ESWT				ULTRASOUND				IONTOPHORESİS				Intergroup Comparisons		
	Pretreatment	Aftertreatment	*Difference*	*p**	Pretreatment	Aftertreatment	*Difference*	*p**	Pretreatment	Aftertreatment	*Difference*	*p**	*p*[1]	*p*[2]	*p*[3]
NRS	4.00 (2.25)	2.00 (3.00)^{a}	2.00 (2.25)^{x}	***<0.001***[†]	5.00 (2.25)	3.00 (2.00)^{a}	2.00 (3.00)^{x}	***0.001***[†]	5.00 (2.00)	1.00 (1.25)^{b}	4.00 (2.25)^{y}	***<0.001***[†]	*0.120*[‡]	***<0.001***[‡]	***<0.001***[‡]
QUİCK DASH	50.5±13.0	38.4±12.1	12.1±13.4	***<0.001***[¥]:	55.6±8.2	40.9±11.2	14.6±11.4	***<0.001***[¥]:	54.4±4.8	40.7±9.2	13.5±8.9	***<0.001***[¥]:	*0.131*	*0.657*	*0.719*
HSG FLEX	22.5 (10.2)	24.0 (9.5)	-1.0 (2.0)^{x}	***0.001***[†]	24.0 (9.0)	25.0 (6.7)	-2.0 (5.2)^{x}	***0.013***[†]	23.0 (7.2)	27.5 (6.0)	-3.5 (4.0)^{y}	***<0.001***[†]	*0.965*[‡]	*0.158*[‡]	***0.001***[‡]
HGS EXT	16.0 (6.5)	17.0 (6.0)^{a}	-1.0 (2.2)^{x}	***<0.001***[†]	16.0 (4.0)	21.5 (8.0)^{b}	-5.5 (7.0)^{y}	***<0.001***[†]	16.0 (1.2)	24.0 (5.0)^{b}	-6.5 (4.5)^{y}	***<0.001***[†]	*0.383*[‡]	***<0.001***[‡]	***<0.001***[‡]
TWO POINTS PINCH	4.00 (2.25)	4.50 (2.25)	-0.50 (1.00)	***0.007***[†]	4.00 (2.25)	4.00 (2.25)	0.00 (0.00)	*0.083*[†]	4.00 (1.25)	4.50 (2.00)	-0.50 (1.00)	***0.024***[†]	*0.617*[‡]	*0.979*[‡]	*0.210*[‡]
THREE POINTS PINCH	3.00 (1.00)	4.00 (1.00)	-1.00 (1.00)	***0.002***[†]	4.00 (2.00)	4.00 (0.25)	0.00 (0.25)	*0.132*[†]	3.00 (1.00)	4.00 (1.25)	-1.00 (1.00)	***0.003***[†]	*0.165*[‡]	*0.514*[‡]	*0.198*[‡]
NHP															
Pain	40.30 (5.00)	30.80 (1.50)	10.15 (10.2)	***<0.001***[†]	40.50 (5.28)	30.80 (1.43)	10.20 (4.40)	***<0.001***[†]	41.65 (3.20)	30.85 (1.65)	10.60 (6.20)	***<0.001***[†]	*0.351*[‡]	*0.861*[‡]	*0.592*[‡]
Physical activity	26.60 (5.30)	12.50 (4.00)	12.50 (5.85)	***<0.001***[†]	26.35 (5.80)	12.60 (2.55)	13.15 (4.18)	***<0.001***[†]	26.20 (4.73)	12.15 (1.88)	13.80 (3.80)	***<0.001***[†]	*0.633*[‡]	*0.723*[‡]	*0.795*[‡]
Sleep	38.50 (1.73)	15.45 (3.65)	22.75 (4.15)	***<0.001***[†]	38.95 (2.48)	16.85 (4.20)	21.75 (5.85)	***<0.001***[†]	38.60 (3.20)	15.60 (3.28)	22.70 (5.28)	***<0.001***[†]	*0.412*[‡]	*0.085*[‡]	*0.855*[‡]
Emotional reactions	42.2 (15.1)	23.1 (3.9)^{a}	18.5 (14.1)^{x}	***<0.001***[†]	42.2 (21.7)	13.8 (2.5)^{b}	27.1 (22.8)^{y}	***<0.001***[†]	42.0 (14.4)	13.5 (2.9)^{b}	28.5 (15.1)^{y}	***<0.001***[†]	*0.928*[‡]	***<0.001***[‡]	***0.009***[‡]
Energy	57.5 (16.6)	42.2 (9.9)	14.0 (17.0)^{x}	***<0.001***[†]	58.5 (7.1)	41.9 (8.9)	19.8 (11.2)^{y}	***<0.001***[†]	61.2 (9.6)	40.7 (7.2)	21.5 (10.8)^{y}	***<0.001***[†]	*0.082*[‡]	*0.797*[‡]	***0.006***[‡]
Social isolation	24.0 (1.3)	17.9 (3.3)^{a}	6.1 (3.5)^{x}	***<0.001***[†]	23.6 (2.0)	13.7 (2.3)^{b}	9.9 (3.2)^{y}	***<0.001***[†]	24.0 (1.3)	11.1 (1.9)^{c}	12.3 (2.2)^{z}	***<0.001***[†]	*0.402*[‡]	***<0.001***[‡]	***<0.001***[‡]
Total	211.39(36.5)	186.42(18.7)	38.7(9.2)	***<0.001***[†]	206.42(32.7)	163.21(15.4)	41.3(13.5)	***<0.001***[†]	213.21(41.6)	151.1(16.2)	47.2(14.1)	***<0.001***[†]	*0.120*[‡]	***<0.001***[†]	***<0.001***[†]

Data are presented as mean±standard deviation for normally distributed variables and median (interquartile range) for non-normally distributed variables. PT: Pre-treatment, TS: Post-treatment, Difference=Pre-treatment-Post-treatment, p*: Pre-.treatment and post-treatment comparisons in each group, p1: Comparison between groups before treatment, p2: Comparison between groups after treatment, p3: Comparison of differences between groups before and after treatment, †: Wilcoxon test, ‡: Kruskal-Wallis Analysis, ¥: Two-way analysis of variance in repeated measures, superscripts a, b and c indicate differences between groups after treatment. x, y and z superscripts indicate the difference in the amount of change between the groups before and after treatment. There is no statistical difference between groups with the same superscripts.

groups (p<0.001). The increase in Hgs ext values in the iontophoresis and US group was statistically higher than in the ESWT group (p<0.001; p<0.001). The increase in Hgs flex values was similar in the iontophoresis and US groups (p=0.908) (Table II). Two points and three points pinch parameters did not show a significant difference before and after treatment in all three groups (two points pinch p=0.617, p=0.979, p=0210), (three points pinch p=0,165; p=0,514; p=0,198).

There was no statistically significant difference between the groups before treatment in terms of quality of life. When the groups were compared within themselves at 1 month after treatment, a significant decrease was found in all treatment groups at all NHP subgroups compared to pretreatment (p<0.001) (Table 2). The efficacy of iontophoresis treatment on NHP total was significantly higher than US and ESWT groups (p<0.001; p<0.001) and US was higher than ESWT (p<0,007). The efficacy of iontophoresis treatment on NHP subgroup social isolation was significantly higher than US and ESWT groups (p<0,001; p=0,022) and US was higher than ESWT (p<0,001). Changes in the NHP subgroup's emotional reaction before and after treatment were statistically different between the groups (p=0.009). Changes in NHP emotional reaction in the US and iontophoresis groups were statistically higher than in the ESWT group (p=0.027; p=0.009). The US and iontophoresis groups were statistically similar (p=0.999). Changes in NHP subgroup energy before and after treatment were statistically different between the groups (p=0.006). The US and iontophoresis groups were statistically higher than the ESWT group (p=0.021; p=0.007). US and iontophoresis groups were statistically similar (p=0.999) (Table II).

Discussion

In this study, we evaluated the effects of ESWT, US, and iontophoresis treatments on pain, grip strength, upper extremity functionality, and quality of life of patients with lateral epicondylitis. All treatment modalities were effective in pain, disability and grip strength, and quality of life before and 1 month after treatment. Iontophoresis was superior to ESWT and US in terms of pain and quality of life. US was superior to ESWT in terms of quality of life. To the best of our knowledge, this is the first study to compare the three different treatment modalities ESWT, US, and Iontophoresis in lateral epicondylitis.

After repetitive movements, elbow pain is a common consequence in the general population (19). The condition tends to affect men and women equally (20). Our study included 38 male patients and 40 female patients. It is more common in individuals over 40 years of age (21). In our study, the average age was 47.96±6.78, consistent with the literature. In a study by Ulusoy et al on 304 patients with elbow pain, they found that the right side was affected in 262 patients and the left side in 42 patients (22). They also demonstrated that the dominant side was affected in 252 of these patients. Another study similarly indicated a higher prevalence of involvement on the dominant side in patients diagnosed with lateral epicondylitis (23). In our study, 93.5% of the patients had right-handed dominancy, and 57.6% of them had right elbow involvement.

Exercise is one of the most common treatment options for patients with LE (24). In a previous study, electrotherapeutic modalities with exercise were more effective than electrotherapy alone, therefore we applied an exercise program to all patient groups (25). The exercises were performed under the supervision of a physiotherapist for ten days. By the way, we ensured that patients performed the exercises correctly and adequately. In our study handgrip strength is improved in all treatment groups; however, we did not investigate the efficiency of the exercise program because there is no control group.

Lateral epicondylitis, resulting from overuse of the tendons, is a painful condition associated with tendinopathy, inflammation, pain, and changes in sensitivity in the lateral elbow. Pain leads to a decrease in grip strength, an impairment of upper extremity function, and a reduction in daily life activities. Lateral epicondylitis is common in the general population; however, there is uncertainty in this area; as numerous randomized controlled trials have not provided conclusive evidence for the nonsurgical treatment modalities. The efficacy of dexamethasone iontophoresis in LE was investigated in previous studies (26-29). In a study comparing dexamethasone iontophoresis and galvanic current in 24 patients with LE, they found that the iontophoresis group had a more significant reduction in pain levels and improved strength and functionality compared to the galvanic current group. [26] Another study with dexamethasone iontophoresis (n=43) showed a significant reduction in pain levels compared to placebo (n=42) and was effective in improving function (27). Akhondali et al compared iontophoresis and Cyriax technique in 22 patients with LE, groups were similarly improved in terms of pain, grip strength, and patient daily activities (28). In a study comparing the effectiveness of iontophoresis and phonophoresis, it was found that iontophoresis was more effective on pain, upper extremity functions, and grip strength (29). Iontophoresis has also been studied in other patient groups. In a study conducted on patients with subacromial impingement syndrome, iontophoresis was found to be more effective in clinical and functional recovery, and also in pain parameters compared to the control group, in another study conducted on patients with knee osteoarthritis, iontophoresis, and galvanic current were found to be more effective in reducing pain than the classical physical therapy program and also iontophoresis was found to be more successful than galvanic current in reducing pain and cyst volume (30,31). This may be the result of the anti-inflammatory effect of dexamethasone.

There is no clear consensus in the literature on the superiority of ESWT and US therapy in LE. In the study by Dedes et al ESWT has been shown to be more effective than US therapy in relieving pain, improving function, and increasing activity in LE (32). Similar results were reported by Kubot et al (33). A meta-analysis suggested that ESWT is superior to US in the treatment of LE (34). However, Yalvaç et al found that while ESWT and US were effective for improving quality of life, upper extremity functioning, grip strength, and reducing pain ESWT was not

superior to US (5). In a previous study, ESWT was combined with topical corticosteroids, there was no significant difference with topical steroids, but pain and hand grip strength improved in both groups (35). In our study, the application of steroids with galvanic current is superior to ESWT.

In the literature, we did not find any study comparing the effectiveness of iontophoresis, ESWT, and US in lateral epicondylitis. In our study, all three treatment modalities were effective in pain and upper extremity functioning, and quality of life compared to pretreatment levels at 1 month follow-up. However, the iontophoresis group showed a significant improvement in pain, upper extremity functioning, and quality of life compared to the ESWT and US groups. When comparing the US and ESWT groups, the improvement in quality of life was higher in the US group.

The limitations of our study include the lack of long-term follow-up, and patients evaluated shortly after the end of the treatment program. The same physical therapy program was applied to all patients and we did not evaluate the effects of physical therapy. Patients were not blinded to the treatment.

The strengths include being conducted at a single center, diagnosis, and treatment initiation by the same physiatrist, and being the only study comparing all three treatment groups. Iontophoresis, US, and ESWT applications have been found to improve pain, function, grip strength, and quality of life in patients with LE. Among these three applications, dexamethasone iontophoresis was superior to the US and ESWT. We believe that studies with a placebo group, involving longer follow-up would be beneficial to examining the effectiveness of treatments.

In conclusion, dexamethasone iontophoresis is more effective in functional and clinical improvement in the treatment of patients with lateral epicondylitis compared to US and ESWT.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Long Term Respiratory Follow up Findings of COVID-19 Cases

COVID-19 Olgularının Uzun Dönem Solunumsal Takip Bulguları

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1510125
Geliş Tarihi | Received: 04.07.2024
Kabul Tarihi | Accepted: 05.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Çoban K, Ayçiçek O, Özlü T. Long Term Respiratory Follow up Findings of COVID-19 Cases. Hitit Medical Journal. 2025;7(1):10-19. doi:10.52827/hititmedj.1510125

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma Karadeniz Teknik Üniversitesi Tıp Fakültesi Bilimsel Araştırmalar Etik Kurulu etik komite tarafından onaylamıştır (Protokol No: 2021/9, Tarih: 28.01.2021).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: TO, KC Tasarım: KC, OA Veri Toplama/Veri İşleme: KC Veri Analizi: KC, OA Makalenin Hazırlanması: KC, OA
Hasta Onamı: Üniversitemiz Klinik Araştırma Etik Kurulu, yayın için hasta onayı gerekmediğini doğrulamıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: The study was reviewed and approved by the Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committee Ethics Committee (Protocol No: 2021/9, Date: 28.01.2021).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: TO, KC Design: KC, OA Data Collection/Data Processing: KC Data Analysis: KC, OA Manuscript Preparation: KC, OA
Informed Consent: Our University Clinical Research Ethics Committee has confirmed that no consent for publication from patients is required.
Financial Disclosure: There are no financial funds for this article.

Long Term Respiratory Follow up Findings of COVID-19 Cases

ABSTRACT

Objective: The aim of this study was to determine the long-term clinical, laboratory and radiologic findings, long-term follow-up findings after acute infection and complications in patients who recovered from COVID-19 infection, especially in patients with insufficient data on long-term effects.

Material and Method: Patients who were admitted to the pulmonology outpatient clinic of our hospital and recovered from COVID-19 infection were included in the study. Demographic data, peripheral oxygen saturation, mMRC score, 6-minute walk test data, ongoing symptoms, laboratory data, radiologic findings and complications during follow-up were recorded. Patients admitted up to the first 4 weeks from the time of diagnosis were grouped as visit 1, patients admitted between 4 and 12 weeks were grouped as visit 2, and patients admitted after 12 weeks were grouped as visit 3.

Results: A total of 520 patients were evaluated, including 190 patients at the first visit interval, 203 patients at the second visit interval and 127 patients at the third visit interval, including duplicate patients. 54% of the participants were female, 46% were male and the mean age was 54 years. Patients had at least one ongoing symptom in 96.3%, 90.6% and 89.8% of the visits, respectively. The most common symptoms were exertional dyspnea, fatigue and cough. The most common pathologic radiographic findings were ground glass opacities in the early period and linear/reticular opacities in the late period. The rates of complications during follow-up were 4.7%, 23.2%, 24.4% according to the visit intervals, respectively and the most common complication was pulmonary fibrosis.

Conclusion: COVID-19 patients; while struggling with the problems associated with the acute disease in the early period, they also have to struggle with persistent symptoms and newly developing complications in the long term. In this context, we think that our study will form a basis for the data of our country and contribute to the literature.

Keywords: COVID-19, long-COVID, post-COVID.

ÖZET

Amaç: Bu çalışmayla özellikle uzun dönem etkileri hakkında yeterli veri olmayan COVID-19 enfeksiyonunu geçirip iyileşen hastaların; uzun dönem klinik, laboratuvar ve radyolojik bulgularının, akut enfeksiyon sonrası uzun vadeli takip bulgularının ve komplikasyonların ortaya konması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya hastanemiz göğüs hastalıkları polikliniğine başvuran, COVID-19 enfeksiyonu geçirip iyileşen hastalar dahil edildi. Hastaların demografik verileri, periferik oksijen satürasyonu, mMRC skoru, 6 dakika yürüme testi verileri, devam eden semptomları, laboratuvar verileri, radyolojik bulguları ve takipte gelişen komplikasyonlar kaydedildi. Tanı anından itibaren ilk 4 haftaya kadar olan sürede başvuran hastalar 1. vizit, 4 ila 12. hafta arasında başvuran hastalar 2. vizit, 12. haftadan sonra başvuran hastalar 3. vizit aralığı olarak gruplandırıldı.

Bulgular: İlk vizit aralığında 190, 2. vizit aralığında 203 ve 3. vizit aralığında 127 olmak üzere mükerrer hastalarla birlikte toplam 520 hasta değerlendirildi. Katılımcıların %54'ü kadın, %46'sı erkek ve ortalama yaş 54'tü. Hastaların, vizit aralıklarına göre sırasıyla %96,3, %90,6, %89,8 oranında devam eden en az bir semptomu mevcuttu. En sık izlenen semptomlar; efor dispnesi, halsizlik, öksürük şeklinde sıralandı. En sık patolojik grafi bulgusu erken dönemlerde buzlu cam opasiteleri iken geç dönemde çizgisel/retikuler opasiteler olarak görüldü. Takipte komplikasyon izlenme oranları vizit aralıklarına göre sırasıyla %4,7, %23,2, %24,4 olarak izlendi ve en sık izlenen komplikasyonun akciğer fibrozisi olduğu görüldü.

Sonuç: COVID-19 hastaları; erken dönemde akut hastalıkla ilişkili sorunlarla mücadele ederken, uzun dönemde de sebat eden semptomlar ve yeni gelişen komplikasyonlarla mücadele etmek zorunda kalmaktadır. Bu bağlamda, çalışmamızın ülkemiz verilerine dayanak oluşturacağını ve literatüre katkı sağlayacağını düşünmekteyiz.

Anahtar Sözcükler: COVID-19, long-COVID, post-COVID.

Introduction

At the end of 2019 in Wuhan city, Hubei province of China; pneumonia cases of unknown cause began to be reported. As a result of the examination of the patients' lower respiratory tract samples, it was understood that the causative agent was a new type of coronavirus and was named 2019 new coronavirus (2019-nCoV) (1). The World Health Organization (WHO) defined the disease COVID-19, which stands for Coronavirus Disease 2019, on February 12, 2020 (2). A pandemic was declared by WHO on March 11, 2020 and as of April 7, 2024, 775,293,630 confirmed cases and 7,044,637 deaths were reported worldwide (3).

While discussions about the follow-up and treatment of acute infection continue, long-term follow-up of patients who have recovered from the disease and the management of complications are also an important problem. Although the literature on the subject is limited, in a comprehensive study Huang et al. shared data as a result of 1-year follow-up of 1276 patients who received inpatient treatment in the hospital with a diagnosis of COVID-19; It was observed that 68% of the participants continued to have at least one complaint after 6 months and 49% after 1 year (4). The most common symptoms were reported respectively as weakness, muscle pain, sleep disturbance and hair loss and it was found to be more common in patients requiring oxygen support and intensive care hospitalization (4). In addition, although multisystemic complications such as lung fibrosis, thromboembolic events, diabetes, hypertension, chronic kidney disease are observed in patients in the long term, the frequency and risk factors of these complications have not been fully elucidated (5).

With this study, patients who have recovered from COVID-19, especially for whom there is not enough data about its long-term effects; It is aimed to reveal long-term clinical, laboratory and radiological findings, long-term follow-up findings and complications after acute infection. Again, during the period when diagnosed with COVID-19, it can be determined whether long-term symptoms and complications develop depending on variables such as age, gender, chronic disease history, severity of the disease and laboratory findings. We aim to use our findings as a reference for the development of long-term follow-up algorithms for COVID-19 patients and recommendations for patient management in the acute period to reduce permanent damage.

Material and Method

Study Design

Our study was conducted between February 2021 and September 2021 after obtaining the approval of the ethics committee. Patients who recovered from COVID-19 infection and applied to our outpatient clinic were included in the study prospectively. This study was obtained from the medical specialty thesis titled 'Long Term Follow up Findings of Covid-19 Cases and Determination of Permanent Disability Status' with ethics committee number 2021/9. Patients over the age of 18 who were diagnosed with SARS-CoV-2 PCR test or with computed tomography and clinical findings and gave written consent to participate in the study were included to this research. Patients who did not meet the inclusion criteria and did not give written informed consent were excluded from the study. When the study was designed, as a result of the evaluations made with the statistical unit in terms of sample size, it was concluded that the number obtained during the study would constitute the final sample since the study was prospective and therefore a standard sample size could not be determined. Demographic data of the patients, peripheral oxygen saturation, mMRC score, 6-minute walking test data, ongoing symptoms, laboratory data, radiological findings (x-ray and computed tomography), complications during follow-up were recorded. Patients who applied within the first 4 weeks from the time of diagnosis were grouped as the 1st visit, patients who applied between 4 and 12 weeks were grouped as the 2nd visit and patients who applied after 12 weeks were grouped as the 3rd visit interval. At the time of admission to the outpatient clinic, patients were admitted to the study at the interval of the visit, taking into account the time elapsed since the time of diagnosis.

Endpoints of the Study

The primary endpoint of our study was determined as the presentation of long-term clinical, laboratory and radiological findings, long-term follow-up findings after acute infection and complications of patients

who had COVID-19 disease and recovered.

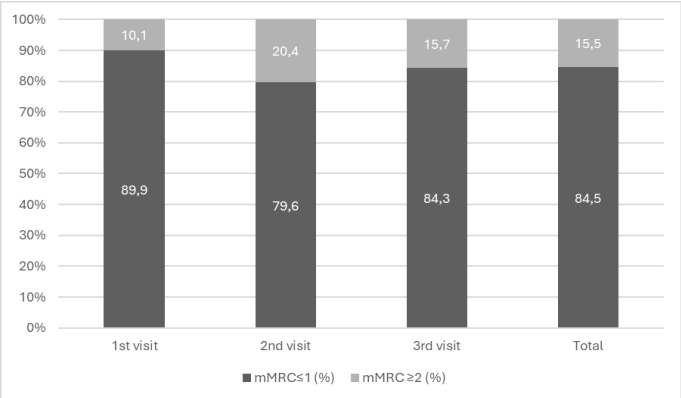
Statistical Analysis

The analysis of the data obtained in the study was performed with the SPSS 23.0 package program. Descriptive statistics were given as arithmetic mean (Mean/Percentage) for measurement variables, standard deviation (SD) and number (n) and percentage (%) for qualitative variables. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the suitability of the data for normal distribution. Comparisons of measurement variables between three independent groups were evaluated with the Kruskal Wallis test in data that did not meet the normal distribution condition. Chi-square test was used to compare qualitative variables in independent groups. Statistical significance level was accepted as $p<0.05$.

Results

A total of 520 patients were included in the study, including 190 patients at the first visit interval, 203 patients at the second visit interval and 127 patients at the third visit interval, including duplicates. The mean admission time from the time of diagnosis was calculated as 25.4(±9.9) days for the first visit interval, 71.1(±18.7) days for the second visit interval and 171(±59.3) days for the third visit interval. The comparison of the demographic data of the patients by groups is given in Table I. No statistically significant difference was observed in the demographic distribution between the groups except for age.

Figure I. mMRC Distribution According to Visit Intervals



mMRC: Modified Medical Research Council

At least 1 symptom was still present in 181 (96.3%) patients who applied to our outpatient clinic at the first visit interval, 184 (90.6%) patients at the second visit interval and 114 (89.8%) patients at the third visit interval. The most frequently described symptoms were exertional dyspnea, fatigue and cough, respectively. The detailed distribution of the frequency of symptoms by visit intervals is given in Table II. At the visits, the patients' Modified medical Research Council Respiratory Scale (mMRC) scores were also evaluated. The mMRC score was classified as 1 and below, 2 and above (Figure I).

Table I. Demographic Data

	1st visit	2nd visit	3rd visit	Total	*p*
Age (Year)	52.4 (±13.4)	54 (±12.9)	56.3 (±14.6)	54 (±13.6)	*0.017*
Gender Female Male	105 (55.3%) 85 (44.7%)	108 (53.2%) 95 (46.8%)	68 (53.5%) 59 (46.5%)	281 (54%) 239 (46%)	0.912
Comorbidities Hypertension Diabetes Mellitus Asthma Thyroid dysfunction Coronary artery disease Heart failure Arrhythmia COPD	 83 (43.7%) 34 (17.9%) 29 (15.3%) 26 (13.7%) 18 (9.5%) 11 (5.8%) 5 (2.6%) 4 (2.1%)	 87 (42.9%) 44 (21.7%) 39 (19.2%) 25 (12.3%) 23 (11.3%) 9 (4.4%) 12 (5.9%) 11 (5.4%)	 56 (44.1%) 16 (12.6%) 16 (12.6%) 12 (9.4%) 19 (15.0%) 5 (3.9%) 7 (5.5%) 7 (5.5%)	226 (43.5%) 94 (18.1%) 84 (16.2%) 63 (12.1%) 60 (11.5%) 25 (4.8%) 24 (4.6%) 22 (4.2%)	
BMI (kg/m²) <30 ≥30	 96 (56.5%) 74 (43.5%)	 104 (56.8%) 79 (43.2%)	 64 (57.1%) 48 (42.9%)	 264 (56.8%) 201 (43.2%)	0.994
Marital status Married Single	 164 (87.2%) 24 (12.8%)	 182 (90.1%) 20 (9.9%)	 117 (92.9%) 9 (7.1%)	 463 (89.7%) 53 (10.3%)	*0.267*
Smoking status Never used Active smoker Quit smoking Passive exposure	 109 (57.4%) 18 (9.5%) 51 (26.8%) 12 (6.3%)	 129 (63.5%) 16 (7.9%) 53 (26.1%) 5 (2.5%)	 73 (57.5%) 12 (9.4%) 38 (29.9%) 4 (3.1%)	 311 (59.8%) 46 (8.8%) 142 (27.3%) 21 (4%)	0.481
Vocation Not working Working Health worker	 131 (68.9%) 59 (31.1%) 22 (11.6%)	 139 (68.5%) 64 (31.5%) 9 (4.4%)	 100 (78.7%) 27 (21.3%) 13 (10.2%)	 370 (71.2%) 150 (28.8%) 44 (8.5%)	*0.94*
Form of diagnosis PCR test CT and clinical	 171 (90.5%) 18 (9.5%)	 195 (96.1%) 8 (3.9%)	 114 (89.8%) 13 (10.2%)	480 (92.5%) 39 (7.5%)	0.132
Previous vaccination Annual flu vaccination Pneumococcal vaccine	 23 (12.6%) 29 (15.8%)	 25 (12.3%) 42 (20.7%)	 9 (7.1%) 25 (19.7%)	 57 (11.1%) 96 (18.7%)	 0.250 0.452
Immunosuppression	14 (7.4%)	12 (5.9%)	5 (3.9%)	31 (6%)	0.449

COPD: Chronic Obstructive Pulmonary Disease, **BMI:** Body Mass Index, **PCR:** Polymerase Chain Reaction, **CT:** Computed Tomography

Within the scope of our study, fingertip oxygen saturations (SpO2) of the patients who applied to our outpatient clinic were measured and grouped by taking a 93% cut-off limit. Accordingly, patients were divided into 94% and above, and 93% and below. 11 (5.9%) of the 185 patients who underwent

SpO_2 evaluation during the first visitwere 93% and below and 174 patients (94.1%) were 94% and above in saturation. In the second visit interval, the number of patients with 93% and below were 24 (12%), 94% and above were 176 (88%); in the third visit interval they were 8 (6.3%) and 119 (93.7%), respectively (*p=0.062*).

Table II. Ongoing Symptoms

	1st visit	2nd visit	3rd visit	Total
Symptom				
Exertional dyspnea	99 (52.4%)	131 (64.5%)	76 (59.8%)	306 (59.0%)
Fatigue	104 (55.0%)	92 (45.3%)	43 (33.9%)	239 (46.1%)
Cough	87 (46.0%)	74 (36.5%)	39 (30.7%)	200 (38.5%)
Chest-back pain	67 (35.4%)	61 (30.0%)	38 (29.9%)	166 (32.0%)
Muscle-joint Pain	31 (16.4%)	31 (15.3%)	6 (4.7%)	68 (13.1%)
Sleep Disturbance	27 (14.3%)	27 (13.3%)	13(10.2%)	67 (12.9%)
Memory Problems	11 (5.8%)	19 (9.4%)	28 (22.0%)	58 (11.2%)
Loss of Taste and Smell	24 (12.7%)	13 (6.4%)	12 (9.4%)	49 (9.4%)
Dyspnea (at rest)	19 (10.1%)	20 (%9.9)	8 (%6.3)	47 (%9.1)
Sputum	15 (7.9%)	17 (8.4%)	10 (7.9%)	42 (8.1%)
Nausea and Vomiting	14 (7.4%)	6 (3.0%)	3 (2.4%)	23 (4.4%)
Loss of Appetite	12 (6.3%)	7 (3.4%)	2 (1.6%)	21 (4.0%)
Excessive Sweating	13 (6.8%)	5 (2.5%)	4 (3.1%)	22 (4.2%)
Headache	11 (5.8%)	7 (3.4%)	1 (0.8%)	19 (3.7%)
Vertigo	6 (3.2%)	6 (3.0%)	2 (1.6%)	14 (2.7%)
Hair loss	3 (1.6%)	4 (2.0%)	6 (4.7%)	13 (2.5%)

Six-minute walking test (6-MWT) was performed on selected patient groups who applied to our outpatient clinic. Start and end saturations (%) and total walking distances (m) were measured. Total walking distances were 397m (±83.2) at visit 1, 363m (±95.5) at visit 2, and 404m (±71.5) at visit 3 and a statistically significant difference was found (*p=0.03*) (Table III).

Another data evaluated in the patients was whether there was weight loss. Weight loss was observed in 76 (51.1%) patients during the first visit, 115 (71.4%) patients during the second visit and 59 (60.2%) patients during the third visit (*p=0.028*). The average weight loss amount was calculated as 3.2kg (±3.6), 7.5kg (± 5.0), 8.6kg (±6.4), respectively, according to the visit intervals (*p=0.00*).

The time to return to normal life, which questioned the time to do daily work or return to the active profession, was 14 days (±7.5), 20.7 days (±15.2), 26.9 days (±26.3), respectively (p<0.05). At the time of the evaluation, 24 (12.6%) patients stated that they could not return to normal life in the first visit interval when the patients were evaluated on the 25.4th day on average, 24 (11.8%) patients in the second visit interval when they were evaluated on the 71.1 th day and 13 (11.2%) patients in the third visit interval when they were evaluated on the 171 st day.

Table III. Six-Minute Walk Test Data

	Start SpO_2 (%)	End SpO_2 (%)	Distance (m)
1st Visit			
93% and below	4 (7.5%)	9 (17%)	397 (±83.2)
94% and above	49 (92.5%)	44 (83%)	
2nd Visit			
93% and below	3 (5.1%)	14 (23.7%)	363 (±95.5)
94% and above	56 (94.9%)	45 (76,3%)	
3rd Visit			
93% and below	4 (6.3%)	11 (17.2%)	404 (±71.5)
94% and above	60 (93.7%)	53 (82.8%)	
Total			
93% and below	11 (6.2%)	34 (19.3%)	388 (±85.1)
94% and above	165 (93.8%)	142 (80.7%)	
p	*0.551*	*0.557*	*0.03*

Intergroup comparisons were made by evaluating the biochemical and radiological findings of the patients at three visit intervals. Among the biochemical parameters, the differences between mean Lymphocyte, Neutrophil, CRP, Procalcitonin, Ferritin, ALT and Creatine kinase (CK) levels were found to be statistically significant. The mean lymphocyte counts according to the groups were calculated as 2215/µl (±1097), 2460/µl (±1072), 2625/µl (±1688) (*p=0.01*). The distribution of neutrophil counts by groups were 5443/µl(±2578), 5177/µl(±4278),4355/µl(±1771) (*p*=0.00). Intergroup CRP levels were 8.1mg/L (±13.3), 7.9mg/L (±14), and 12.1mg/L (±66.2), respectively(*p=0.018*). Procalcitonin levels were calculated as 0.04µg/L (±0.03), 0.18µg/L (±1.03), 0.03µg/L (±0.02) (p=0.044). According to the groups, ferritin levels were 158.8µg/L (±178.9), 167.8µg/L (±261.8), 75.5µg/L(±70.1) (*p=0.001*). According to the visit intervals, ALT levels were 36U/L (±28.3), 32U/L (±41.6), 24.5U/L (±21.1) (*p=0.00*), while CK levels were 71.7U/L (±63.3), 80.7U/L (±72.0), 102.6U/L (±59.0) (*p=0.00*) (Table IV).

Table IV. Laboratory Results by Visit Intervals

	1st visit	2nd visit	3rd visit	Total	Normal range	*p*
Laboratory						
Leucocyte	8439	8199	7133	8223	3710-10190 /µl	*0.452*
Hemoglobin	13.6	13.6	13.9	13.7	12.89-16.73 g/dL	*0.225*
Platelets	282	265	259	271	130-400 103/µl	*0.258*
Neutrophil	5443	5177	4355	5074	1910-7080 /µl	*0.000*
Lymphocyte	2215	2460	2625	2410	1200-3600 /µl	*0.001*
CRP	8.1	7.9	12.1	9.0	< 5 mg/L	*0.018*
Procalcitonin	0.04	0.18	0.03	0.1	< 0.5 µg/L	*0.044*
Glucose	108	114	101	109	70-100 mg/dL	*0.159*
Creatinine	0.79	0.79	0.82	0.8	0.67-1.17 mg/dL	*0.237*
BUN	16.8	16.3	16.5	16.5	6-20 mg/dL	*0.474*
ALT	36	32	24.5	31.7	0-45 U/L	*0.000*
AST	24.5	23.1	21.6	23.2	0-35 U/L	*0.107*
GGT	42.4	55.8	25.1	42.8	0-55 U/L	*0.000*
LDH	223	230	205	222	<248 U/L	*0.075*
CK	71.7	80.7	102.6	82.4	20-200 U/L	*0.000*
D-Dimer	0.7	1.3	0.8	0.9	0-0.55mg/L	*0.555*
Ferritin	158.8	167.8	75.5	140.8	23.9-336.2 µg/L	*0.001*
TSH	1.8	2.5	2.1	2.2	0.34-5.6 µIU/mL	*0.864*

CRP: C-Reactive Protein, **BUN:** Blood Urea Nitrogen, **ALT:** Alanine Aminotransferase, **AST:**Aspartate Aminotransferase**, GGT:** Gamma Glutamyl Transferase**, LDH:** Lactate Dehydrogenase, **CK:** Creatinin Kinase, **TSH:** Thyroid Stimulating Hormone

Patients who applied to our outpatient clinic were evaluated radiologically by chest radiography and if clinically necessary computed lung tomography (CT). Pathological x-ray findings were detected in 74 (41.6%) patients at the first visit, pathological x-ray findings were observed in 65 (35.3%) patients at the second visit and 26 (21.8%) patients at the third visit (p=0.02).

Table V. Chest X-Ray Findings

	1st visit	2nd visit	3rd visit	Total	*p*
Pathological Finding	74 (41.6%)	65 (35.3%)	26 (21.8%)	165 (34.3%)	*0.02*
Ground Glass Opacity	52 (29.2%)	50 (27.2%)	7 (5.9%)	109 (22.7%)	*<0.01*
Consolidation	13 (7.3%)	8 (4.3%)	1 (0.8%)	22 (4.6%)	*0.032*
Linear/Reticular Opacity	33 (18.5%)	44 (23.9%)	22 (18.5%)	99 (20.6%)	*0.364*
Atelectasis	21 (11.8%)	18 (9.8%)	13 (10.9%)	52 (10.8%)	*0.826*
Bronchiectasis	4 (2.2%)	2 (1.1%)	4 (3.4%)	10 (2.1%)	*
Peripheral Localization	54 (30.3%)	55 (29.9%)	23 (19.3%)	132 (27.4%)	*0.073*
Central Localization	2 (1.1%)	17 (9.2%)	1 (0.8%)	20 (4.2%)	*
Bilateral Distribution	48 (27.0%)	60 (32.6%)	23 (19.3%)	131 (27.2%)	*0.04*
Multilobar Distribution	26 (14.6%)	31 (16.8%)	19 (16.0%)	76 (15.8%)	*0.84*
Subpleural Distribution	18 (10.1%)	37 (20.1%)	12 (10.1%)	67 (13.9%)	*0.009*

*: p value could not be given

While the most common pathological x-ray finding in the first visit interval was ground- glass opacities (n=52, 29.2%), similarly, ground-glass opacities were the most common in the second visit interval (n=50, 27.2%). The most common pathological radiographic finding in the third visit interval was linear/reticular opacities (n=22, 18.5%) (Table V).

The distribution of ground-glass opacities, which is the most common CT finding, according to visit intervals was 11 (61.1%), 13 (54.2%), and 9 (40.9%). The distribution of linear-reticular opacities was 7 (38.9%),9 (37.5%) and 14 (63.6%) patients. The distribution of other findings by visit intervals is detailed in Table VI.

Table VI. Distribution of CT Findings

	1st Visit	2nd Visit	3rd Visit	Total
Pathological Finding	16 (88.9%)	17 (70.8%)	20 (90.9%)	53 (82.8%)
Ground Glass Opacity	11 (61.1%)	13 (54.2%)	9 (40.9%)	33 (51.6%)
Linear/Reticular Op.	7 (38.9%)	9 (37.5%)	14 (63.6%)	30 (46.9%)
Atelectasis	6 (33.3%)	7 (29.2%)	6 (27.3%)	19 (29.7%)
Bronchiectasis	3 (16.7%)	6 (25.0%)	6 (27.3%)	15 (23.4%)
Interlobular Septal Thickening	-	4 (16.7%)	7 (31.8%)	11 (17.2%)
Crazy Paving Sign	-	-	5 (22.7%)	5 (7.8%)
Pulmonary Nodule	-	7 (29.2%)	5 (22.7%)	12 (18.8%)
Lymphadenopathy (LAP)	-	2 (8.3%)	2 (9.1%)	4 (6.3%)
Consolidation	1 (5.6%)	1 (4.2%)	-	2 (3.1%)
Pleural Effusion	1 (5.6%)	-	1 (4.5%)	2 (3.1%)
Honey Comb	-	-	2 (9.1%)	2 (0.4%)
Peripheral Localization	11 (61.1%)	14 (58.3%)	18 (81.8%)	43 (67.2%)
Bilateral Distribution	10 (55.6%)	14 (58.3%)	17 (77.3%)	41 (64.1%)
Multilobar Distribution	10 (55.6%)	13 (54.2%)	12 (54.5%)	35 (54.7%)
Subpleural Distribution	1 (5.6%)	11 (45.8%)	8 (36.4%)	20 (31.3%)

Different rates of pulmonary and extrapulmonary complications were observed in the patient groups included in the study. Complications were observed in 9 (4.7%) of the participants evaluated in the first visit interval, 47 (23.2%) in the second visit interval and 31 (24.4%) in the third visit interval (*p<0.005*). The most common complication was lung fibrosis and it was detected in 38 (18.7%) patients in the second visit interval and 20 (15.7%) patients in the third visit interval. DM was observed at a rate of 6(3.2%) in the first visit interval, 11 (5.4%) in the second visit interval and 7 (5.5%) in the last visit interval. Pulmonary thromboembolism (PTE) and venous thromboembolism (VTE) were observed in 1 (0.5%) patient at the first visit interval, 4 (2.0%) patients at the second visit interval and 7 (5.5%) patients at the third visit interval (Table VII).

Table VII. Disturbution of Complications

	1st visit	2nd visit	3rd visit	Total
Complication	9 (4.7%)	47 (23.2%)	31 (24.4%)	68 (13.1%)
Pulmonary Fibrosis	-	38 (18.7%)	20 (15.7%)	58 (11.2%)
Diabetes Mellitus (DM)	6 (3.2%)	11 (5.4%)	7 (5.5%)	24 (4.6%)
PTE/VTE	1 (0.5%)	4 (2%)	7 (5.5%)	12 (2.3%)
Hypertension	2 (1.1%)	1 (0.5%)	2 (1.6%)	5 (1.0%)
CRF	-	-	1 (0.8%)	1 (0.2%)
GI Bleeding	-	1 (0.5%)	-	1 (0.2%)
Avascular Necrosis	-	-	1 (0.8%)	1 (0.2%)
Proteinuria	1 (0.5%)	-	-	1 (0.2%)
Hypothyroidism	-	-	1 (0.8%)	1 (0.2%)

PTE: Pulmonary Thromboembolism, **VTE:** Venous Thromboembolism, **CRF:** Chronic Renal Failure,

GI: Gastrointestinal

Discussion

Although the severity of the COVID-19 pandemic,

which causes significant mortality and morbidity worldwide, has been greatly reduced, we may still encounter patients with SARS-CoV-2. Knowing the long-term effects of this infection on the lungs in patients who have had the infection and recovered is important for both pandemic period patients and follow-up of new cases. For this purpose, in our study, we tried to define the demographic data, comorbidities, ongoing symptoms, laboratory and radiological findings and developing complications of patients who had acute infection and recovered and applied to our outpatient clinic.

In the study conducted by Huang et al. with discharged COVID-19 patients, in which 1733 patients were evaluated at an average of 6 months after symptom onset; 68% of the patients stated that they still had an ongoing symptom and this rate was even higher in those with severe illness. Ongoing symptoms were, in order of frequency, fatigue and muscle pain, sleep disturbance, hair loss and inability to smell (6).

In another study by Carfi et al., patients were evaluated at an average of 60.3 days from the onset of symptoms after discharge and symptom questioning was performed. In this study, which included a total of 143 participants, only 12.6% of patients reported that all symptoms disappeared, 32% reported that 1 or 2 symptoms persisted and 55% reported that 3 or more symptoms persisted. The most common symptoms were weakness, shortness of breath, joint pain and chest pain, respectively (7). In a meta-analysis evaluating long-term COVID symptoms, the most common symptoms were pain, fatigue, neurocognitive symptoms, shortness of breath and palpitations (8).

In our study, 96.3%, 90.6% and 89.8% of the patients admitted to the outpatient clinic had ongoing symptoms according to the visit intervals. The most common symptoms were exertional dyspnea, fatigue, cough, chest and back pain, fatigue, muscle and joint pain. The fact that symptoms such as shortness of breath, exertional dyspnea and fatigue were observed more frequently in the last visit interval was thought to be related to the fact that patients who had a more severe illness in the 3rd visit interval and whose respiratory complaints still persisted presented to the outpatient clinic more frequently. Forgetfulness and memory problems were observed in 5.8% at the first visit and increased to 9.4% and 22.0% at subsequent visits, respectively. It was also found that sleep problems, muscle joint pain, taste and smell complaints were also common. In a review evaluating the neurological and neurocognitive outcomes of Long Covid, fatigue, headache, sleep disturbances, muscle weakness and muscle pain were the most common symptoms (9). The persistence of muscle and joint pain, sleep disturbances, forgetfulness and memory blurring symptoms at approximately 6 months from the time of diagnosis were considered as components of Post Covid-19 Neurologic Syndrome (PCNS), on which studies are ongoing (10).

In our study, mean lymphocyte and neutrophil counts, CRP, procalcitonin, ferritin, ALT and creatine kinase (CK) levels were found to be statistically significant according to the visit intervals of patients admitted to our outpatient clinic. In a systematic review of 34 relevant studies, it was observed that serum C-reactive protein (CRP), interleukin-6 (IL-6), lactate dehydrogenase (LDH), D-dimer levels were more elevated in critically ill patients (11). In addition, increased total white blood cell count was observed as a poor prognostic factor, while a decrease in the agranulocytic series, including lymphocytes and monocytes, was associated with poor disease prognosis. LDH levels were found to be higher in patients followed up in intensive care unit (11). In a case-control study by Gameil et al. in which patients' laboratory findings were evaluated at least 3 months after PCR negativity, erythrocyte sedimentation rate, CRP, D-dimer, ALT, AST, GGT and ALP levels were significantly higher in the case group (12). D-dimer is a biomarker of fibrinolytic system and coagulation activation. In a French review of 71 studies, increased D-dimer levels (3-4 times the upper limit of normal) were associated with poor prognosis and mortality in COVID-19 (13). No statistically significant difference was observed between the mean D-dimer levels of the patients included in our study. However, the fact that D-dimer levels were still above the upper limit of normal at all visit intervals and especially at the 3rd visit interval when the patients were evaluated at approximately 6 months suggests that the coagulation and fibrinolytic system has not yet reached physiologic limits in patients.

The mean CRP levels of the patients evaluated in our study were found to be higher than the upper normal limit of 5 mg/L in all visit intervals and it was observed to be higher especially in the 3rd visit interval. This was thought to be related to the fact that patients who applied to our outpatient clinic in the 3rd visit interval, in which the participants were evaluated at an average of approximately 6. months, had more severe illnesses and had higher hospitalization rates.

In a review comparing 70 studies evaluating ferritin levels in Covid-19 patients, it was observed that ferritin levels were higher in severe disease [(95% CI 306.51-489.02), *p <.001*], and significantly higher in patients who died compared to those who survived [(95% CI 391.01-963.33), *p <.001*] (14). In addition, a systematic review comparing inflammatory markers of COVID-19 patients with and without Post Covid syndrome showed no significant difference in ferritin levels between the two groups (15). In our study, although mean serum ferritin levels were normal at all visit intervals, a statistically significant decrease was observed at later visit intervals, suggesting that it may be associated with disease severity in the early period.

In a study in which a total of 384 patients were evaluated at an average of 8 weeks after discharge, 333 (87%) patients had chest radiographs and 85% had pathologic radiographic findings. 56% of the radiographs were typical for Covid-19 and 29% were indeterminate (16). In an another study in which patients were evaluated radiologically at the time of diagnosis and 3 months later, the most common radiologic findings in the early period were ground-glass opacities and consolidation, while reticular opacities were observed much more frequently at 3 months (17). In our study, the rates of pathological radiography according to the visit intervals were 41.6%, 35.3% and 21.8%, respectively. While ground glass opacities were dominant in the first visit interval, it was observed that they were replaced by linear/reticular opacities and atelectasis in the following visit intervals.

In a study conducted in China in which long-term CT findings were also evaluated, HRCT was performed in 353 patients evaluated at 6 months from symptom onset and 186 (53%) patients had at least one pathologic CT finding (6). In a systematic review evaluating the radiological findings of Long COVID patients, the most common tomography finding was ground-glass opacities, followed by fibrotic/interstitial abnormalities (18). In our study, a relatively limited number of CT scans were performed within clinical necessity. The most common pathologic CT findings are ground-glass opacities, linear/reticular opacities and atelectasis. While ground glass opacities are more common in the early period, linear/reticular opacities are more common CT findings in the later period.

Especially in severe COVID-19 patients, respiratory complications and lung fibrosis are observed due to diffuse lung involvement, macrophage activation syndrome, excessive immune response and subsequent ARDS, advanced age, intensive care follow-up and mechanical ventilation (19). This suggests that patients with severe disease and survivors are at risk for pulmonary fibrosis in the future. In a meta-analysis of 69 studies from 15 different countries, shortness of breath, cough, lung dysfunction and pulmonary fibrosis were the most common complications after COVID-19 (20). In a study by Stewart et al. in which patients were evaluated at a mean of 240 days after discharge, residual lung anomalies were found in 166 (79.4%) of 209 patients, with ground glass opacities in 25.5% and reticulation in 15.1% (21). In the patients we evaluated in our study, respiratory distress and pulmonary fibrosis were commonly seen. In the follow-up of the patients, patients who were still ongoing after the 12 th week and thought to be associated with lung fibrosis and whose radiological findings such as linear, reticular opacities, traction bronchiectasis and honeycomb were observed, were evaluated as post-COVID lung fibrosis. In this context, lung fibrosis was considered in 38 (18.7%) patients in the second visit interval and 20 (15.7%) patients in the third visit interval. Although it is observed to be relatively less at the last visit interval, it is thought that the level of persistence of respiratory symptoms and fibrosis needs to be evaluated with longer follow-up.

Stress hyperglycemia, impaired glucose tolerance and the use of drugs that impair glycemic control, especially corticosteroids, stand out as facilitating factors for the development of Diabetes Mellitus (DM)

in COVID-19 patients (22). In our patients we followed up, DM was observed to develop in 6(3.2%) patients in the first visit interval, 11 (5.4%) in the second visit interval and 7 (5.5%) in the last visit interval. It is thought that DM developed in our patients due to frequent use of corticosteroids, possibly impaired fasting glucose, and stress-related factors.

COVID-19 patients are at risk for increased thromboembolic events, macrovascular and microvascular thromboses (23). In a meta-analysis, it was found that venous thromboembolism (VTE) was approximately 30%, deep vein thrombosis (DVT) was 20% and pulmonary thromboembolism (PTE) was 18% in COVID 19 patients (24). In our study, PTE/VTE was observed in 0.5%, 2% and 5.5% according to the visit intervals, while gastrointestinal bleeding was observed in 1 (0.5%) patient in the 2nd visit interval. It is thought that seasonal influenza vaccine and pneumococcal vaccines will provide a milder course of Covid-19, a shorter length of stay in the intensive care unit and a decrease in the need for mechanical ventilation, especially by preventing secondary respiratory infections, but there is not enough evidence in this regard (25,26). In our study, a statistically significant difference was found between those who were vaccinated with pneumococcal or annual influenza vaccines and those who were not vaccinated in terms of service hospitalization rates in the total population (49.2% vs. 38.8%, *p=0.042*). Although no significant difference was observed in other subgroups in this respect, it was observed that the hospitalization rates were generally higher in the vaccinated groups. This was thought to be related to the fact that the vaccinated population was generally over 65 years of age and had higher additional comorbidities and high overall hospitalization rates. At the beginning of the study, it was planned to evaluate the patients included in the first visit interval at other visit intervals with ongoing follow-ups. However, we had patients who could not come to the next visits due to reasons such as patients avoiding coming to the hospital due to the pandemic and patients whose complaints regressed did not want to reapply. Our study was conducted as a cross-sectional study, not a follow-up study.

Since our study was planned prospectively, the risk of data loss was minimized. However, in the follow-up data of patients who were followed up in external centers and then applied to our outpatient clinic (despite the use of platforms such as e-nabız etc.), sometimes deficiencies were observed, especially in the data related to the acute disease period.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Neuroprotective Effects of Dexmedetomidine in Acute Carbon Monoxide Intoxication: An Experimental Study

Akut Karbonmonoksit İntoksikasyonunda Deksmedetomidin'in Nöroprotektif Etkileri: Deneysel Bir Çalışma

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1485232
Geliş Tarihi | Received: 15.05.2024
Kabul Tarihi | Accepted: 13.10.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Büyükkeskin H, Doğan G, Kayır S, et al. Neuroprotective Effects of Dexmedetomidine in Acute Carbon Monoxide Intoxication: An Experimental Study. Hitit Medical Journal 2025;7(1):20-28. https://doi.org/10.52827/hititmedj.1485232

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Ankara Eğitim ve Araştırma Hastanesi Hayvan Deneyleri Yerel Etik Kurulu tarafından onaylanmıştır. (Onay No: 2022-0073).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: HB, GD, SK, ÖY Tasarım: SK, AK, SÖÖ Veri Toplama/Veri İşleme: HB, GD, ÖY Veri Analizi: EA, YK, SÖÖ Makalenin Hazırlanması: HB, GD, SK, EA, YK, AK.
Hasta Onamı: Gerek yoktur
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Bilgi: Bu makale bir tıbbi uzmanlık tezinden türetilen bir yayındır ve başka bir dergiye sunulmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Local Ethics Committee for Animal Experiments of Ankara Training and Research Hospital (Approval No: 2022-0073).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: HB, GD, SK, ÖY Design: SK, AK, SÖÖ Data Collection/Data Processing: HB, GD, ÖY Data Analysis: EA, YK, SÖÖ Manuscript Preparation: HB, GD, SK, EA, YK, AK.
Informed Consent: Not applicable
Financial Disclosure: There are no financial funds for this article.
Information: This article is a publication derived from a medical speciality thesis and has not been submitted to any other journal.

Neuroprotective Effects of Dexmedetomidine in Acute Carbon Monoxide Intoxication: An Experimental Study

ABSTRACT

Objective: It is aimed to evaluate the neuroprotective effects of Dexmedetomidine (DEX), which has antioxidant, antiapoptotic, anti-inflammatory properties, in acute carbon monoxide toxicity.

Material and Method: 28 Wistar-Albino female rats were randomly divided into four groups as control, Carbon monoxide (CO) poisoning, CO poisoning + DEX and DEX only. The rats in the study groups were exposed to 3000 ppm CO for 30 minutes. DEX was administered half an hour after the onset of CO exposure. At the end of the experiment, blood and tissue samples were taken from the sacrificed rats. Bcl-2 Immunopositively cell values in tissue samples taken from prefrontal and hippocampal areas were scored by examining immune expressions of Bcl-2 antibodies obtained by immunohistochemical method under light microscope. Malondialdehyde (MDA), nitric oxide (NO), asymmetric dimethylarginine ADMA levels, superoxide dismutase (SOD), and catalase (CAT) activity values were measured from blood and right hemisphere brain tissue samples by biochemical methods.

Results: CAT, SOD, MDA, ADMA and NO values were statistically different between the experimental groups (*p<0.001*). According to the post-hoc pairwise comparison test results, there was no statistical difference in any parameter between the DEX group alone and the control group (*p>0.05*). CAT, SOD and NO, and Bcl-2 immunosuppressive cell levels were decreased in the CO group compared to the control group (*p<0.001* in all), while ADMA and MDA levels increased (*p<0.001* in all). CAT, SOD, and NO levels were statistically higher in the CO + DEX group compared to the CO group (*p:0.007; p:0.028; p:0.017, respectively*).

Conclusion: DEX administered half an hour after CO poisoning increases antioxidant structures such as CAT, SOD and NO. Accordingly, DEX may have a neuroprotective effect for carbon monoxide poisoning.

Keywords: Carbon monoxide, dexmedetomidine, neuroprotective effect.

ÖZET

Amaç: Antioksidan, antiapopitotik, antiinflamatuar özellikleri olan Deksmedetomidin'in (DEX) akut karbonmonoksit (CO) toksikasyonunda nöroprotektif etkilerinin değerlendirmesi amaçlanmıştır.

Gereç ve Yöntem: 28 adet Wistar-Albino dişi sıçan kontrol, CO zehirlenme, CO zehirlenme + DEX ve sadece DEX olmak üzere rastgele dört gruba ayrıldı. Çalışma gruplarındaki sıçanlar 3000 ppm konsantrasyonda CO'e 30 dakika boyunca maruz bırakıldı. DEX CO maruziyetinden yarım saat sonra uygulandı. Deney bitiminde sakrifiye edilen sıçanlardan kan ve doku örnekleri alındı. Prefrontal ve hipokampal alanlardan alınan doku örneklerinde Bcl-2 İmmunopositif hücre değerleri immunohistokimyasal yöntem ile elde edilen Bcl-2 antikorların immune ekspresyonlarının ışık mikroskobu altında incelenmesi ile skorlandı. Alınan kan ve sağ hemisfer beyin doku örneklerinden biyokimyasal yöntemlerle malondialdehit (MDA), nitrik oksit (NO), asimetrik dimetilarjinin (ADMA) düzeyleri ile süperoksit düsmutaz (SOD) ve katalaz (CAT) aktivite değerleri ölçüldü.

Bulgular: Deney grupları arasında CAT, SOD, MDA, ADMA ve NO değerleri istatistiksel olarak farklı idi (*p<0,001*). Post-hoc ikişerli karşılaştırma test sonuçlarına göre yalnız DEX grubu ve kontrol grubu arasında hiçbir parametrede istatistiksel fark yoktu (*p>0,05)*. CO grubunda CAT, SOD ve NO ve Bcl-2 immünsüpresif hücre düzeyleri kontrol grubuna göre azaldı (tamamında *p<0,001*) ve ADMA ve MDA düzeyleri arttı (tamamında *p<0,001*). CO + DEX grubunda CO grubuna göre CAT, SOD ve NO düzeylerini istatistiksel olarak daha yüksekti (*sırasıyla p:0,007; p:0,028; p:0,017*).

Sonuç: CO zehirlenmesinden yarım saat sonra uygulanan DEX CAT, SOD ve NO gibi antioksidan yapıları arttırır. Buna bağlı olarak DEX'in CO zehirlenmesi için nöroprotektif bir etkisi olabilir.

Anahtar Sözcükler: Deksmedetomidin, karbonmonoksit, nöroprotektif etki.

Introduction

Carbon monoxide (CO) is a colorless, odorless, and poisonous gas that occurs as a result of incomplete combustion of carbon-based fuels and substances. It is the most common lethal poison worldwide and frequently leads to neurological sequelae as the most common morbidity (1,2). CO has an affinity for hemoglobin (Hb) approximately 250 times that of oxygen. By reversible binding with the iron in hemoglobin, CO forms carboxyhemoglobin (COHb), reducing the capacity of oxygen transport in the blood and decreasing oxygen delivery to tissues (3).

The pathophysiological mechanisms of CO toxicity are classified into hypoxic and cellular theories. CO induces hypoxia by forming COHb and shifting the oxygen-hemoglobin dissociation curve to the left. This leads to hypoxia due to reduced oxygen delivery to tissues, resulting in decreased tissue perfusion and adverse effects on various systems such as cardiac function and neuropsychological function (4). CO poisoning can cause ischemic and hypoxic brain damage in survivors by inducing damage to oxygen distribution and mitochondrial oxidative phosphorylation (5). Brain damage may arise from various factors including neurotoxicity, acidity, electrolyte imbalance, depolarization, oxidative stress, nitric oxide stress, inflammation, and cellular death (6).

Dexmedetomidine (DEX) is a selective α2 receptor agonist routinely used for sedation and anesthetic applications in clinical practice. Unlike most sedatives, DEX induces conscious sedation in patients with its reversible sedative effect, allowing easy arousal (7). Due to its ability to provide conscious sedation, DEX is commonly used in awake craniotomy. Additionally, it possesses anxiolytic and analgesic potentials (8). DEX causes less respiratory depression compared to other sedatives, but there may be an increased risk of hypotension and bradycardia. Particularly, caution should be exercised in using this drug in patients with hepatic impairment due to its involvement in DEX pharmacokinetics (9). However, DEX exhibits neuroprotective effects by reducing inflammation, apoptosis, autophagy, preserving the blood-brain barrier, reducing brain edema, and maintaining cellular structure (10).

The hypothesis of this study is that the administration of DEX to rats exposed to CO poisoning may exert a neuroprotective effect. Based on this hypothesis, this study aimed to evaluate the effects of CO exposure and DEX administration on the activities of antioxidant enzymes catalase (CAT) and superoxide dismutase (SOD), the levels of malondialdehyde (MDA) as the end product of membrane lipid peroxidation, asymmetric dimethylarginine (ADMA) levels indicating endothelial damage, and nitric oxide (NO) levels, as well as the distribution of B-cell lymphoma gene 2 (Bcl-2), known as anti-apoptotic and antioxidant, in brain tissue through immunohistochemical analysis. The study aimed to compare these parameters and evaluate the neuroprotective effects of DEX in acute carbon monoxide intoxication.

Material and Method

This study was conducted after obtaining approval from the Local Ethics Committee for Animal Experiments of University of Health Sciences Ankara Training and Research Hospital (Approval No: 2022-0073). This study was conducted in accordance with our country's animal rights regulations and international animal welfare standards. All animals used in the study were cared for in accordance with the highest level of welfare standards before and during the experiment, and all necessary precautions were taken to prevent unnecessary pain, suffering or harm. A total of 28 female Wistar albino rats, weighing an average of 250 grams, were obtained from the Experimental Animals Laboratory of Ankara Education and Research Hospital for use in this study. The carbon monoxide gas utilized in the experiment was prepared by HABAŞ Industrial and Medical Gases Industry Inc. in Izmit, and it contained CO at a concentration of 3000 ppm.

Formation of Experimental Groups

The experimental animals were kept under laboratory conditions and fasted for 12 hours. The rats were randomly selected using a lottery system and grouped to apply the procedures outlined below:

Group 1: Control group (n=7); consisting of 7 rats, placed in the experimental chamber and exposed to room air for 30 minutes. Euthanasia was performed at the end of the 30th minute, and blood and tissue samples were collected.

Group 2: Dexmedetomidine group (n=7); comprising 7 rats, this group received intraperitoneal DEX (10 µg/kg/min) 30 minutes before being placed in the experimental chamber. They were exposed to room air for 30 minutes. Euthanasia was performed at the end of the 30th minute, and blood and tissue samples were collected.

Group 3: CO poisoning group (n=7); consisting of 7 rats, this group was placed in the experimental chamber. Rats placed in the experimental chambers were exposed to CO gas at a concentration of 3000 ppm for 30 minutes at a flow rate of 3 liters/minute, creating CO poisoning. Euthanasia was performed at the end of the 30th minute, and blood and tissue samples were collected.

Group 4: CO poisoning + Dexmedetomidine group (n=7); comprising 7 rats, this group was placed in the experimental chamber and exposed to CO gas at a concentration of 3000 ppm for 30 minutes at a flow rate of 3 liters/minute, creating CO poisoning. Afterward, intraperitoneal DEX (10 µg/kg/min) was administered for 30 minutes. Subsequently, euthanasia was performed, and blood and tissue samples were collected.

Immunohistochemical Analysis

In this study, Tissues obtained from the prefrontal and hippocampal regions were fixed in formalin and left for at least one day before undergoing paraffin embedding. Paraffin embedding involved tissue tracking, followed by sectioning with a microtome to obtain 5 µm thick sections, which were then placed on slides. These sections were then incubated overnight at 54°C. After incubation, the sections underwent two rounds of 20-minute deparaffinization in xylene to remove paraffin. Subsequently, the sections were rehydrated by passing through a series of decreasing alcohol concentrations (100%, 90%, 80%, and 70%). Following rehydration, the sections were washed twice with fetal calf serum (PBS) and then subjected to microwave irradiation in 250 ml freshly prepared citric acid buffer (pH: 6.0) to expose antigenic epitopes. After microwave treatment, the sections were cooled at room temperature for 20 minutes and then washed three times for five minutes each with PBS at room temperature.

Next, to saturate endogenous peroxidase activity in the tissue, the sections were incubated in a 3% H_2O_2 solution at room temperature for 20 minutes. The sections were washed three times for five minutes each with PBS and then incubated with blocking solution at room temperature for 7 minutes to block nonspecific bindings. After removal of the blocking solution, the samples were incubated overnight at +4°C in a humid environment with anti-bcl-2 antibodies. Appropriate isotype control antibodies or sera were used as negative controls, ensuring they were of the same concentration as the primary antibodies. Following incubation with the primary antibodies, the sections were subjected to three 5-minute washes and the sections were then incubated with biotinylated secondary antibodies for 45 minutes at room temperature.

After the incubation with biotinylated secondary antibodies, the tissue samples were incubated with streptavidin-peroxidase complex at room temperature for 30 minutes. After washing with PBS, diaminobenzidine solution was added to visualize the antigen-antibody complexes, and after washing with water, they were counterstained with Mayer's hematoxylin. The samples were then dehydrated through increasing alcohol series, clarified in xylene, and cover slipped with mounting solution. Subsequently, the chromogenic reaction of the antibodies was examined for immunoexpressing under a light microscope. Immunoexpressing was scored semi-quantitatively as 0 for no expression, 1 for weak expression, 2 for moderate expression, and 3 for strong expression. Statistical analysis was performed to evaluate whether there was a difference between groups using the Mann-Whitney U test.

Collection and Preparation of Blood and Tissue Samples

The rats were sacrificed, and blood samples were collected via intracardiac puncture into biochemical tubes. The biochemical blood samples were centrifuged at 1500 rpm for 10 minutes to separate the sera, which were aliquoted.

Brain tissues were removed, washed with saline solution, and the right hemispheres were weighed. Then, they were immediately frozen in liquid nitrogen and stored at -80°C.

At the time of analysis, all tissue samples were homogenized in 1/6 phosphate buffer (pH: 7.4) using a blade homogenizer, and then centrifuged at 20,000

Table I. Comparison of laboratory parameters according to rat groups by ANOVA test

	Control (1)	Dex (2)	CO (3)	Dex + CO (4)	*P*	*Post-hoc P*
CAT (IU/ml)	4.21±0.89	4.47±0.3	1.22±0.50	3.02±0.94	*<0.001**	1-3: <0.001 2-3: <0.001 *2-4: 0.033* *3-4: 0.007*
SOD (U/ml)	1.13±0.17	1.34±0.35	0.39±0.14	0.85±0.30	*<0.001**	*1-3: <0.001* *2-3: <0.001* *2-4: 0.018* *3-4: 0.028*
MDA (nmol/ml)	1.13±0.25	1.32±0.29	2.48±0.51	2±0.40	*<0.001**	*1-3: <0.001* *1-4: 0.004* *2-3: <0.001* *2-4: 0.030*
ADMA (µmol)	119.7±70.42	129.3±41.85	359.8±87.75	299.2±88.09	*<0.001**	*1-3:<0.001* *1-4: 0.002* *2-3<0.001* *2-4: 0.004*
NO (µmol/g)	52.87±8.99	47.05±9.08	24.10±8.36	39.1±3.83	*<0.001**	1-3: <0.001 1-4: 0.031 2-3: <0.001 3-4: 0.017

*: ANOVA ve Post-hoc Tukey test

rpm for 10 minutes to separate the supernatants.

Biochemical Parameters

Total protein levels in all homogenates and supernatants were determined spectrophotometrically using the Bradford method. MDA levels in homogenates were assessed using the ELISA method. The activity levels of SOD and CAT in supernatants were determined using commercial kits, whereas NO and ADMA levels were determined using the ELISA method. To normalize enzyme activity values, they were divided by the protein values in the supernatants.

Statistical Analysis

Statistical analyses were performed using the SPSS program (Version 22.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation. The normal distribution of groups was assessed using the Shapiro-Wilk test. Since the data were normally distributed, statistical comparison of numerical measurements among independent groups of more than two was conducted using one-way analysis of variance (ANOVA). Post-hoc Tukey test was performed for pairwise comparisons to determine which groups showed differences after ANOVA. A *p-value < 0.05* was considered statistically significant.

Results

According to the results of the ANOVA test, CAT, SOD, MDA, ADMA, and NO values were statistically significantly different among the experimental groups (*p<0.001*). Post-hoc pairwise comparison test results revealed that CAT and SOD values in the control and DEX groups were significantly higher than those in the CO group. Additionally, CAT and SOD values in the DEX group were significantly higher than those in the DEX + CO group. CAT and SOD values in the CO group were significantly lower than those in the DEX + CO group (Table I).

Table II. Comparison of Bcl-2 Immunopositive cells values according to rat groups by ANOVA test

Control (1)	Dex (2)	CO (3)	Dex+ CO (4)	*P*	Post-hoc P	
Bcl-2 İmmunopositive cells (U/ml)	31.07±6.83	25.35±5.81	13.42±3.76	18.18±3.85	*<0.001**	1-3: <0.001 1-4: 0.002 2-3: 0.004

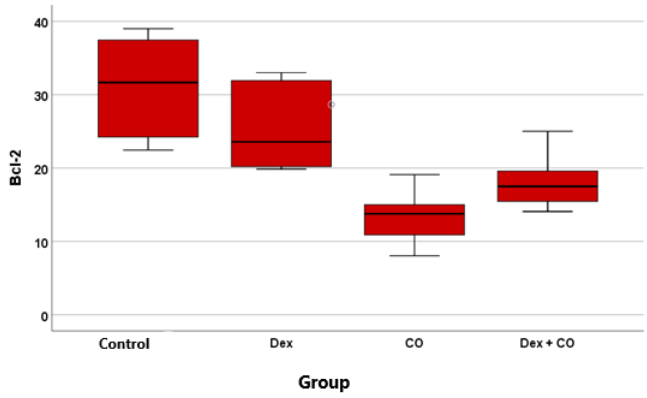
*: ANOVA ve Post-hoc Tukey test

According to post-hoc pairwise comparison test results, MDA and ADMA values in the control and DEX groups were significantly lower than those in the CO group. Additionally, MDA and ADMA values in the DEX group were significantly lower than those in the DEX + CO group. MDA and ADMA values in the CO group were significantly higher than those in the DEX + CO group (Table I).

Based on the post-hoc pairwise comparison test results, it was found that NO values in both the control and DEX groups were significantly higher compared to the CO group. Furthermore, NO values in the control group were notably higher than those in the DEX + CO group. Conversely, NO values in the

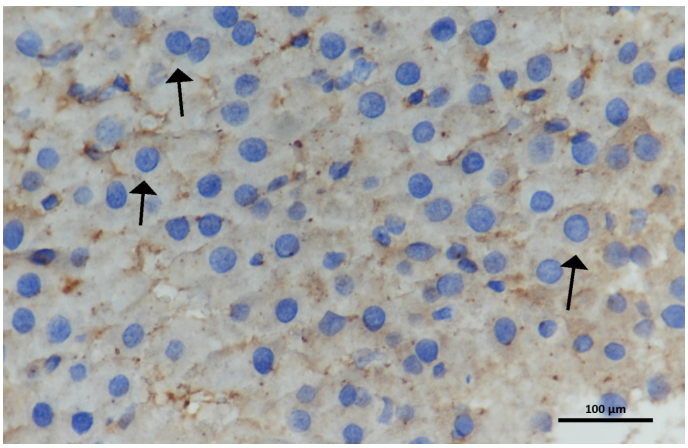
CO group were significantly lower than those in the DEX + CO group (Table I).

Figure I. Box plot showing the distribution of Bcl-2(U/ml) immunopositive cells between groups



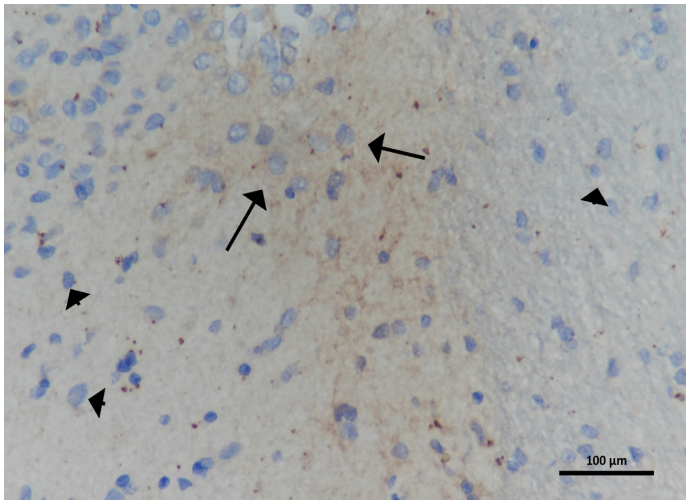
According to the results of the ANOVA test, there were statistically significant differences in the values of Bcl-2 immunopositively cells among the experimental groups (*p<0.001*). Post-hoc pairwise comparison test results showed that Bcl-2 immunopositively cells values in the control and DEX groups were significantly higher than those in the CO group. Additionally, Bcl-2 immunopositively cells values in the control group were significantly higher than those in the DEX + CO group (Table II). The distribution of Bcl-2 immunopositively cells values among groups is presented in Figure I.

Figure II. Cells stained strongly positive for anti-bcl-2 in control group brain section (arrow), bar 100 µm



In the immunostaining conducted with the anti-Bcl-2 antibody in the hippocampus, widespread expression of Bcl-2 (indicated by arrows) was observed in the control group. (Figure II). The DEX + CO group brain section showed areas with moderate positive staining of anti-bcl-2 (arrow) and areas with no staining (arrowhead) (Figure III).

Figure III. Area with cells stained moderately positive for anti-bcl-2 (arrow) and unstained cells (arrowhead) in DEX + CO group brain section, bar 100 µm



Discussion

In this study examining the consequences of CO poisoning, the neuroprotective effects of DEX application were assessed. After CO poisoning, CAT, SOD, and NO levels significantly decreased, while MDA and ADMA levels significantly increased. However, in rats treated with DEX after CO poisoning, CAT, SOD, and NO levels were found to be significantly higher compared to rats exposed to CO poisoning alone. Therefore, it is considered that DEX contributes to the antioxidant response following CO intoxication. MDA is the end product of arachidonic acid and larger polyunsaturated fatty acids, decomposed via enzymatic or non-enzymatic pathways. MDA shows a good correlation with the degree of lipid peroxidation (11). According to some studies, MDA functions both as a regulator and a messenger of gene expression. Excessive MDA production has been considered an indicator of oxidative stress in some research, and it has been associated with various pathological conditions such as Alzheimer's disease, cancer, cardiovascular diseases, diabetes, liver diseases, and Parkinson's (12-13). In our study, plasma MDA levels, indicative of oxidative stress, significantly increased after CO exposure, while this increase was not statistically significant with DEX administration, although it decreased.

Antioxidants are specialized defense systems in the body. For a compound to be a good antioxidant, it should not be converted into a reactive radical and should have a specific target. The most important group of antioxidants is SOD. SOD utilizes free radicals as substrates and converts superoxide into H_2O_2. The SOD enzyme is an enzyme that helps protect against the harmful effects of oxygen and superoxide radicals. The distribution of this enzyme should be investigated together with CAT because the product formed after the reaction catalyzed by SOD needs to be removed by CAT to prevent the accumulation of oxygen, which is one of the toxic species. Therefore, it is important to examine the distribution of this enzyme with CAT. CAT is found in peroxisomes and is effective on H_2O_2. CAT accelerates the conversion of H_2O_2 into water and oxygen. SOD and CAT enzymes are considered among the most active antioxidant enzymes in living organisms and are found in all tissues, cells, and intracellular organelles of aerobic organisms. These enzymes play an important role in the maintenance of life (14). Some studies have shown that individuals with low CAT levels are more susceptible to diseases such as type 2 diabetes and hypertension and are affected by diseases such as thickening of arterial walls and tumor formation (15). In our study, it was observed that the antioxidant enzymes CAT and SOD decreased significantly after CO intoxication, and that these enzymes increased significantly after DEX administration following CO intoxication.

NO, which has important functions including vasodilatation and release of inflammatory cytokines and is synthesized by the endothelium, has complex functions in various tissues. Among these functions, it is involved in immunity, nonspecific immunity, inhibition of viral replication and transplant rejection (16). In the nervous system, NO is associated with memory, learning, epilepsy, pain sensitivity and neurodegeneration. In the respiratory system, it is involved in bronchodilatation, asthma and ARDS pathogenesis. In our study, NO levels decreased statistically significantly in rats with CO intoxication but increased statistically significantly in rats given DEX after CO intoxication.

ADMA is an endogenous inhibitor of nitric oxide synthase (NOS), suppressing its activity. As ADMA levels increase, nitric oxide (NO) production decreases. It has been reported that ADMA-induced endothelial dysfunction plays a role in atherosclerosis and can be used as a marker (17). High ADMA levels in patients are believed to result from endothelial insufficiency. The mechanism of endothelial dysfunction caused by ADMA involves reduced vascular NO production and increased vascular superoxide levels (18). In our study, while ADMA levels, indicating endothelial damage, statistically significantly increased in rats with CO intoxication, this increase was statistically not significant after DEX application following CO intoxication.

Bcl-2 is an intracellular membrane protein and is also described as anti-apoptotic and antioxidant. The distribution of this protein differs according to cell type. Bcl-2 is known to have antioxidant properties by reducing lipid peroxidation and to provide resistance against H_2O_2-induced apoptotic death. One of the most widely accepted is that Bcl-2 is a substance that acts as an antioxidant and reduces ROS production (19). Studies conducted to investigate the expression and amount of bcl-2 in different regions of the brain and in various organs and tissues show contradictory results in the natural aging process. This may be due to differences in the cell-specific activity of bcl-2 and survival conditions (20). Kaufmann et al. showed that bcl-2 levels were increased in the hippocampus and cerebellum of aged rats and this increase may be related with the increased age-related oxidative stress level and antioxidant properties of bcl-2 (21). In our study, it was observed that Bcl-2 level, which is also known as anti-apoptotic and antioxidant, decreased significantly in rats given CO, whereas this decrease was more limited with DEX administration after CO intoxication, although not statistically significant.

Although CO intoxication is a common condition, research is ongoing for its treatment. Zengin et al. investigated the neuroprotective effects of amantadine after CO intoxication (22). In their study, they found a statistically significant decrease in NMDA levels with amantadine administration after CO intoxication compared to CO intoxication. Although CAT, SOD, ADMA, NO and Bcl-2 levels were not statistically significant, clinically significant results were obtained. Investigation of oxidant and antioxidant systems,

determination of the severity of poisoning, prediction of post-poisoning outcomes and the search for new markers that can be used as well as the choice of treatment are also important in toxicology. There is evidence that acute antioxidant augmentation may be effective as a new therapeutic strategy to prevent delayed neurological problems in CO poisoning, that CO-mediated brain damage is a result of free radical cascade and that the balance between the antioxidant system and oxidative stress is in a strong relationship (23). Several mechanisms have been associated with the neuroprotective function of dexmedetomidine, including neurotransmitter regulation, inflammatory response, oxidative stress, apoptotic pathway, autophagy, mitochondrial function and other cell signalling pathways. Therefore, dexmedetomidine has been reported to have the potential to be a novel neuroprotective agent for a wide range of neurological disorders (24). Also Chen L et al; DEX protects against diabetic hyperglycaemia-induced cerebral I/R injury through attenuation of oxidative stress, inflammation and apoptosis (25).

In conclusion; when brain mechanisms are considered, brain damage caused by many causes such as hypoxia, free oxygen radicals, inflammation and cell destruction after CO exposure is very complex. The decrease in Bcl-2 level after CO exposure shows that cell destruction increases and the increase in ADMA, which indicates endothelial damage, shows that vascular structures are also impaired after hypoxia. DEX administration has a limited effect to prevent this process in CO poisoning. Dexmedetomidine administered half an hour after CO poisoning increases antioxidant structures such as CAT, SOD and NO. Accordingly, DEX may have a neuroprotective effect for CO poisoning.

More comprehensive studies are required to better understand CO intoxication and its treatment and to evaluate the neuroprotective effects of DEX and the relationship between the oxidant and antioxidant system with CO intoxication and hypoxia. This will lead to new developments in the treatment of CO intoxication.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Diagnostic Comparison of MRI Sequences for Assessing Myometrial Invasion in Endometrial Cancer: A 1.5T MRI Study

Endometrium Kanserinde Miyometrial İnvazyonun Değerlendirilmesinde MRG Sekanslarının Tanısallığının Karşılaştırması: 1.5T MRG Çalışması

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1559453
Geliş Tarihi | Received: 02.10.2024
Kabul Tarihi | Accepted: 11.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Akçay A, Peker AA. Diagnostic Comparison of MRI Sequences for Assessing Myometrial Invasion in Endometrial Cancer: A 1.5T MRI Study. Hitit Medical Journal 2025;7(1):29-36. https://doi.org/10.52827/hititmedj.1559453

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 12/06/2024 tarihinde Bezmialem Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2024/280.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: AA Tasarım: AA Veri Toplama/Veri İşleme: AA, AAP Veri Analizi: AA Makalenin Hazırlanması: AA, AAP
Hasta Onamı: Çalışma retrospektif bir çalışma olarak dizayn edildiğinden çalışma için bilgilendirilmiş onam formuna gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Bezmialem Vakıf University Non-Interventional Research Ethics Committee on 12/06/2024. Decision no: 2024/280.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: AA Design: AA Data Collection/Data Processing: AA, AAP Data Analysis: AA Manuscript Preparation: AA, AAP
Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.
Financial Disclosure: There are no financial funds for this article.

Diagnostic Comparison of MRI Sequences for Assessing Myometrial Invasion in Endometrial Cancer: A 1.5T MRI Study

ABSTRACT

Objective: To compare the diagnostic accuracy of T2-weighted, dynamic contrast-enhanced imaging, and diffusion-weighted imaging in assessing myometrial invasion depth in endometrial cancer and to determine if any sequence performs better.

Material and Method: In this retrospective study, 98 patients with histopathologically confirmed endometrial cancer underwent preoperative multiparametric pelvic magnetic resonance imaging scans using a 1.5-T machine between January 2018 and May 2024. The T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging sequences were independently reviewed by an experienced radiologist blinded to pathology results to assess myometrial invasion depth (superficial vs. deep). Sensitivity, specificity, accuracy, negative predictive value, and positive predictive value were calculated. Statistical analyses included ROC curves and McNemar's test.

Results: T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging showed high diagnostic accuracy for assessing myometrial invasion, with area under the curve values of 0.967, 0.954, and 0.916, respectively. T2-weighted images achieved the highest sensitivity (1.0) and specificity (0.934). While diffusion-weighted images and dynamic contrast-enhanced images demonstrated slightly lower accuracy compared to T2-weighted images, the differences were not statistically significant ($p>0.05$). However, both diffusion-weighted images and dynamic contrast-enhanced images had higher misclassification rates in cases with fibroids, adenomyosis, or indistinct junctional zones.

Conclusion: All three magnetic resonance sequences demonstrated high diagnostic accuracy for evaluating myometrial invasion in EC. Although T2-weighted images had slightly better diagnostic accuracy due to its superior anatomical detail, the differences were not statistically significant. In cases with confounding factors, combining T2-weighted, dynamic contrast-enhanced, and diffusion-weighted imaging improves diagnostic reliability.

Keywords: Endometrial cancer, MRI, myometrial invasion.

ÖZET

Amaç: T2 ağırlıklı, dinamik kontrastlı görüntüleme ve difüzyon ağırlıklı görüntüleme tekniklerinin endometrial kanserde miyometrial invazyon derinliğini değerlendirmedeki tanısal doğruluğunu karşılaştırmak ve herhangi bir dizinin daha iyi performans gösterip göstermediğini belirlemektir.

Gereç ve Yöntem: Bu retrospektif çalışmada, Ocak 2018 ile Mayıs 2024 tarihleri arasında histopatolojik olarak doğrulanmış endometrium kanseri tanısı konulan 98 hastaya preoperatif multiparametrik pelvik manyetik rezonans görüntülemeleri yapıldı. T2 Ağırlıklı, dinamik kontrastlı ve difüzyon ağırlıklı görüntüleme dizileri, patoloji sonuçlarından habersiz deneyimli bir radyolog tarafından bağımsız olarak incelenerek miyometrial invazyon derinliği (yüzeyel veya derin) değerlendirildi. Duyarlılık, özgüllük, doğruluk, negatif prediktif değer ve pozitif prediktif değer hesaplandı. İstatistiksel analizler ROC eğrileri ve McNemar testi ile yapıldı.

Bulgular: T2 Ağırlıklı, dinamik kontrastlı ve difüzyon ağırlıklı görüntüleme dizileri, miyometrial invazyonun değerlendirilmesinde yüksek tanısal doğruluk gösterdi; eğri altındaki alan değerleri sırasıyla 0,967, 0,954 ve 0,916 olarak bulundu. T2 Ağırlıklı seri, en yüksek duyarlılık (1,0) ve özgüllük (0,934) değerlerine ulaştı. Difüzyon ağırlıklı görüntüleme ve dinamik kontrastlı görüntüleme, T2 Ağırlıklı seriye kıyasla daha düşük doğruluk gösterdi, ancak aradaki fark istatistiksel olarak anlamlı değildi ($p>0,05$). Bununla birlikte, Difüzyon ağırlıklı görüntüleme ve dinamik kontrastlı görüntülemede, fibroid, adenomyozis veya belirsiz junctional zone gibi karışıklığa neden olan faktörler daha fazla yanlış sınıflandırmaya yol açmıştır.

Sonuç: Üç manyetik rezonans dizisi de endometrium kanserinde miyometrial invazyonun değerlendirilmesinde yüksek tanısal doğruluk göstermiştir. Daha fazla anatomik detay sunan T2 Ağırlıklı serinin, daha yüksek tanısal doğruluk sağladığı gözlemlenmiş; ancak diğer sekanslarla istatistiksel olarak anlamlı fark saptanmamıştır. Karışıklığa neden olan durumlarda, T2 Ağırlıklı serinin difüzyon ağırlıklı görüntüleme ve dinamik kontrastlı görüntüleme ile birlikte değerlendirilmesi tanısal doğruluğu artırmak için önerilmektedir.

Anahtar Sözcükler: Endometrium kanseri, MRG, miyometrial invazyon.

Introduction

Endometrial cancer (EC), frequently observed in older, postmenopausal women, is among the most prevalent gynecologic malignancies (1). Most cases of EC are diagnosed early, when the disease is limited to the uterus, due to the common symptom of vaginal bleeding (2). The surgical procedure and clinical management of EC are determined according to the stage of the disease. The pathological staging of EC is assessed using the FIGO classification system (3). In advanced EC, treatment may be extended with neoadjuvant chemotherapy and pelvic lymph node dissection, along with standard hysterectomy and bilateral salpingo-oophorectomy (2). Deep myometrial invasion, high cellular grade, cervical involvement, parametrial extension, lymph node metastasis, and the aggressive histological subtype of the tumor are critical factors indicating a poor prognosis and necessitating extensive surgical procedures in EC (2, 4). In cases with superficial myometrial invasion, if there are no other high-risk criteria present, hysterectomy and bilateral salpingo-oophorectomy are sufficient in terms of treatment (2). The diagnosis of EC is assessed through endometrial sampling using a Pipelle biopsy or dilation and curettage (D&C). Although preoperative endometrial biopsy has higher accuracy in detecting the degree of myometrial invasion, tumoral heterogeneity and insufficient sampling of the tumor tissue may lead to an underestimation of the stage of the disease (5). Magnetic resonance imaging (MRI) exhibits high soft tissue resolution, particularly when utilizing small field of view multiparametric scanning protocols. In this case, according to the guidelines, MRI is recommended for assessing endometrial cancer before surgery (2). Several studies in the literature have assessed MRI's accuracy in detecting the degree of myometrial invasion (6-9). Some studies evaluated MRI performance in a single session, while others evaluated the performance of two different MRI sequences separately. This study aims to individually assess all multiparametric pelvic MRI (mp-MRI) sequences, such as T2-weighted (T2W), diffusion-weighted (DWI), and contrast-enhanced T1-weighted (DCE) imaging, and to see if one works better than the others. Due to factors such as myometrial thinning, adenomyosis, and uterine fibroids, these MRI sequences may be affected, potentially leading to incorrect determinations regarding the degree of myometrial invasion.

Material and Methods

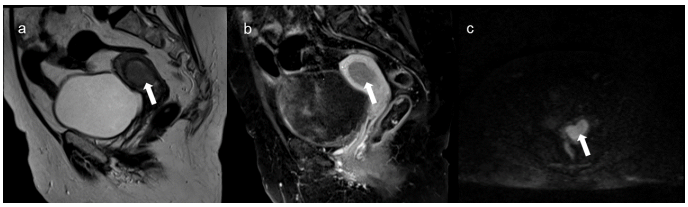
Approval for this study was obtained from Bezmialem Vakıf University Non-Interventional Research Ethics Committee (E-54022451-050.04-155766). Patients diagnosed with endometrial cancer who underwent preoperative pelvic mp-MRI between January 2018 and May 2024 were included. All subjects underwent surgery within five weeks after the MRI was obtained. Patients management was aligned with the ESMO guidelines (5). The exclusion criteria for this study included: 1. Significant image artifacts 2. Prior neoadjuvant chemotherapy 3. Tumors too small to be detected on MRI. All hysterectomy specimens were evaluated according to FIGO criteria, and the degree of myometrial invasion (superficial (<50%) and deep (>50%)) was compared with the findings from the individual multiparametric pelvic MRI sequences including T2W, DWI, DCE images. The MRIs were interpreted by an experienced abdominopelvic radiologist with six years of expertise, who was blinded to the histopathologic results. A total of 120 patients were initially considered for the study. However, 11 were excluded due to neoadjuvant chemotherapy, eight were excluded because of significant image artifacts, and five were excluded because their tumors were too small to detect on MRI. Ultimately, 98 patients were included in the study.

mp-MRI protocol

MRI scans were performed using a 1.5-T Siemens Avanto system. Patients were instructed to fast for a minimum of four hours before the procedure. No antispasmodic drugs were administered, and the patients' bladders were kept mildly distended throughout the process. The imaging protocol included T2-weighted images in the axial, coronal, and sagittal planes. For axial images, the TR/TE values were set at 5190/108, for coronal images at 4450/108, and for sagittal images at 4290/108. The field of view (FOV) was 420 mm for the axial and coronal planes, and 450 mm for the sagittal plane. The slice thicknesses were 5 mm, 4 mm, and 4.5 mm, respectively. Additionally, diffusion-weighted

imaging (DWI) was obtained with b-values of 50, 400, and 800 s/mm^2. The TR/TE value was 6600/81, with a FOV of 420 mm and a slice thickness of 5 mm. T1-weighted axial images (TR/TE: 716/10; FOV: 420 mm) were acquired both before and after contrast administration. Fat-saturated T1-weighted axial images were also taken using the same parameters. Gadolinium-diethylenetriamine pentaacetic acid was injected intravenously at a dose of 0.1 mmol/kg body weight. Afterward, contrast-enhanced images were obtained in the axial, coronal, and sagittal planes.

Figure I. The T2W image showed a hyperintense expansive mass in the endometrial cavity with no deep myometrial invasion, delineated from the hypointense junctional zone (a). The lesion appeared hypointense and distinct from the myometrium on the DCE image (b), and hyperintense with diffusion restriction, also clearly separated from the myometrium, on the DWI image (c).

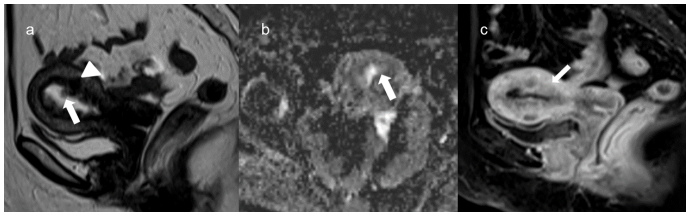


Analysis of MR images

Mp-MRI retrieved from the hospital database system were evaluated using a workstation. An experienced abdominopelvic radiologist with six years of experience interpreted the MRI scans and scored the degree of myometrial invasion (either superficial or deep) for each sequence.

On T2W images, the tumor showed an intermediate signal intensity, presenting as hypointense relative to the myometrium and hyperintense relative to the endometrium (Figure I). Tumor borders were carefully assessed in three T2-weighted plans simultaneously, especially when the tumor was close to uterine fibroids or adenomyosis with junctional zone enlargement. This was done to ensure accurate estimation of the depth of myometrial invasion, avoiding both underestimation and overestimation (Figure II). The tumor boundaries were determined by comparing the hyperintense signal intensity on DWI relative to the myometrium with the corresponding hypointense signal intensity on the ADC map. It was established whether the myometrial invasion was less than or greater than 50%. In DCE images, the tumor tissue, which appeared hypointense and exhibited less contrast enhancement compared to the myometrium, was identified to determine the degree of myometrial invasion. The boundaries of the EC within the myometrium were defined based on the signal characteristics described for each sequence. Following this, it was determined whether the myometrial invasion was less than or greater than 50%.

Figure II. The T2W image demonstrates a polypoid isointense mass within the endometrial cavity adjacent to hypointense adenomyomatosis, without evidence of myometrial invasion (a). Axial DWI reveals an iso-hyperintense lesion clearly delineated from the myometrium (b). The presence of adenomyosis, exhibiting a similar contrast-enhancement pattern as the mass, results in pseudo-invasion appearance into deeper myometrial layers(c).

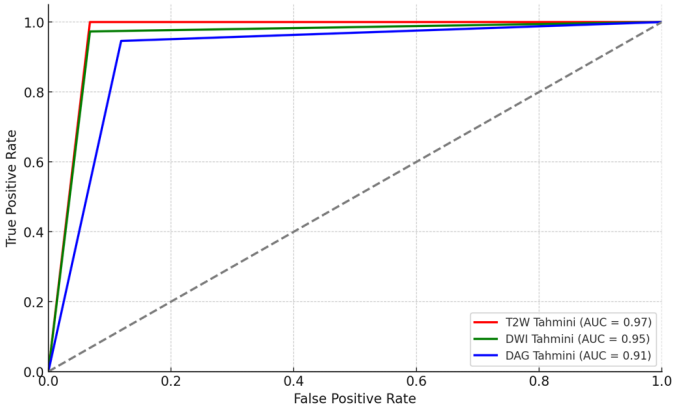


Statistical analysis

The statistical analysis in this study focused on evaluating the effectiveness of the T2W, DWI, and DCE MRI sequences in predicting the depth of myometrial invasion in cases of endometrial cancer. Continuous variables, such as patient age and tumor size, were described using measures like means, medians, and standard deviations. Age differences between patients with superficial and deep myometrial invasion were compared using an independent t-test. Diagnostic performance metrics, including sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV), were calculated for each MRI sequence. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was reported along with 95% confidence intervals. To evaluate differences in diagnostic performance between sequences, McNemar's test was used, with statistical significance set at $p<0.05$. All analyses were conducted using SPSS software (IBM Corp.,

Version 28.0, 2021) and MedCalc version 19.6.1.

Figure III. ROC curves for T2W, DWI, and DCE sequences in predicting the depth of myometrial invasion.



Results

Among the 98 cases analyzed in this study, 61 (62%) presented with superficial myometrial invasion, while 37 (38%) exhibited deep myometrial invasion, as confirmed by pathological findings. The overall average age was 60.76 years, with a median age of 61 years. The average tumor size was 31.69 mm, with a median size of 28.5 mm.

The average age for patients with superficial myometrial invasion was 59.05 years (SD = 10.63), and the median age was recorded as 59 years. Conversely, the mean age of patients with deep myometrial invasion was 63.57 years (SD = 11.81), while the median age was 65 years. Although there was a noticeable difference in age distributions, the independent t-test showed that this difference was not statistically significant (*p=0.053*)

This study evaluated the effectiveness of T2W, DWI, and DCE MR sequences in estimating the extent of myometrial invasion in cases of endometrial cancer (Table I). The T2W sequence showed the best performance, with a sensitivity of 1.0, specificity of 0.934, and positive and negative predictive values (PPV and NPV) of 0.902 and 1.0, respectively (*p<0.001*). The DWI sequence also showed high performance, with sensitivity, specificity, PPV, and NPV of 0.973, 0.934, 0.900, and 0.983, respectively (*p<0.001*). Although the DCE sequence exhibited lower performance compared to the other sequences, it still demonstrated satisfactory results, with values of 0.946, 0.885, 0.833, and 0.964, respectively (*p<0.001*).

Accuracy rates for the T2W, DWI, and DCE sequences were similarly high, at 0.972, 0.965, and 0.938, respectively. ROC analysis revealed AUC values for T2W, DWI, and DCE of 0.967 (95% CI: 0.932–0.992), 0.954 (95% CI: 0.908–0.984), and 0.916 (95% CI: 0.855–0.957), respectively (Figure III). Cohen's Kappa analysis indicated strong agreement between the sequences, with values of 0.958 for T2W, 0.947 for DWI, and 0.905 for DCE. The pairwise comparison of the MRI sequences revealed p-values of 0.7272 for the comparison between T2W and DWI, 1.0000 for T2W and DCE, and 0.6875 for DWI and DCE, indicating no statistically significant differences in their performances.

Regarding misclassifications, T2W overestimated 1 case (false positive) and underestimated 1 case (false negative). DWI overestimated 2 cases and underestimated 1 case, while DCE exhibited the highest discrepancy, with 4 overestimated and 2 underestimated cases. In cases of incorrectly staged tumors on MRI, confounding factors such as cornual location (n = 2), concomitant adenomyomatosis (n = 2), and the presence of myoma uteri (n = 1) were identified.

Discussion

This study evaluated the diagnostic accuracy of T2W, DWI, and DCE MR sequences in determining the depth of myometrial invasion in cases of endometrial cancer. Our findings indicated that all three sequences provided high diagnostic accuracy, with T2W

Table I. Diagnostic performance of MR sequences in predicting depth of myometrial invasion

MR sequences	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	AUC	p value
T2W	100	93.4	97.2	90.2	100	0.967	*<0.001*
DWI	97.3	93.4	96.5	90.0	98.3	0.954	*<0.001*
DCE	94.6	88.5	93.8	83.3	96.4	0.916	*<0.001*

PPV: positive predictive value, NPV: negative predictive value, AUC: area under the curve, T2W: T2 weighted imaging, DWI: diffusion-weighted imaging, DCE: dynamic contrast-enhanced imaging

demonstrating the highest overall performance. These results are consistent with the study that highlights the critical role of T2W MRI in accurately delineating myometrial invasion (10,11). There were no substantial differences noted in the performances of the sequences. However, obtaining images on three axes and the high contrast resolution helped better delineate anatomical boundaries, especially in challenging tumors located in the cornual region where the myometrium is thin. This is thought to have contributed to the higher success rate of the T2W sequence.

Similarly, a study conducted with 3T MRI reported, similar to our findings, that while there was no statistically significant difference in the performance of the sequences, DWI showed better diagnostic performance than T2W images (12). This difference may be attributed to the higher technical capacity of 3T MRI machines, which provide a better signal-to-noise ratio and improved contrast resolution.

DWI demonstrated a 97% accuracy rate with an AUC of 0.954 in predicting the degree of myometrial invasion, which is consistent with the literature (13). Studies in the literature have reported that diagnostic performance improves when DWI sequences are evaluated in conjunction with T2W sequences (14,15). Although in this study each sequence was assessed separately, it is predicted that a combined evaluation with T2W could enhance diagnostic performance due to its high contrast resolution and signal-to-noise ratio. In the literature, a study similar to ours reported no significant difference between DWI and DCE in determining the extent of myometrial invasion (16). However, a meta-analysis demonstrated that DWI was superior to DCE in detecting the depth of myometrial invasion (17). This finding is thought to be related to technological advancements that have improved the contrast resolution of DWI. Additionally, DWI enables differentiation between malignant tumors and benign lesions such as uterine fibroids and adenomyosis, which may exhibit similar contrast enhancement to tumors but, unlike tumors, do not show diffusion restriction. These factors likely contribute to the superior performance of DWI in detecting myometrial invasion. Additionally, in our study, it was observed that in tumors with cornual localization, particularly in postmenopausal patients with myometrial thinning, assessment errors may arise when relying solely on axial DWI. This highlights the importance of high-resolution T2W imaging obtained in three planes, which proved to be more effective in accurately determining the depth of myometrial invasion in such cases.

DCE images showed an accuracy of 94% and an AUC of 0.916 in evaluating the extent of myometrial invasion in endometrial cancer. Additionally, as highlighted in previous studies, the absence of interruption in early-phase subendometrial enhancement plays a key role in identifying tumors confined to the endometrial cavity, which holds particular significance in the planning of fertility-sparing surgeries (18). Although the other two sequences (T2W, DWI) exhibited better diagnostic performance, the difference in diagnostic accuracy was not statistically significant. Conditions such as fibroids, adenomyosis, and an indistinct junctional zone led to misinterpretation of myometrial invasion depth on DCE. Similar to our findings, the study by Beddy et al. also reported that DCE images could result in incorrect radiological assessments in the presence of accompanying lesions, while DWI showed better performance (13). Therefore, since accompanying lesions with contrast enhancement patterns similar to EC that are located near the tumor-myometrium interface may lead to misinterpretation on DCE images, DWI and T2W images should be used to assist in the evaluation of these cases.

Preoperative staging in EC is essential for predicting patient prognosis and guiding treatment decisions (2,4). Assessment of myometrial invasion depth using MRI in the preoperative setting has been integrated into clinical guidelines for EC (2,19). In our study, all imaging sequences demonstrated high diagnostic accuracy for evaluating myometrial invasion depth, with no significant differences in AUC values 0.967, 0.954, and 0.916 for T2W, DWI, and DCE, respectively. However, in a few cases where discrepancies between sequences were observed, T2W images showed the highest concordance with pathology results. While there is no clear consensus in the literature, our findings from a 1.5T MRI indicate that the high-resolution T2W sequence may be more effective than the others (10-12). This is likely because it provides superior anatomical detail and

allows for evaluation across multiple planes. DWI and DCE, which offer functional insights into tumor biology, are also important components of the EC imaging protocol, and our results indicate that these sequences provide comparable diagnostic accuracy to T2W. However, in cases where factors such as cornual location, fibroids, adenomyosis, or an indistinct junctional zone may lead to inaccurate assessment of myometrial invasion depth, it is crucial to evaluate all sequences together for accurate staging.

There are several limitations to this study. First, the study was performed with a 1.5-T MRI scanner, which may have influenced diagnostic performance when compared to 3T MRI systems, known for their higher resolution and better signal-to-noise ratio. Second, the study did not evaluate interobserver variability, as all MRI sequences were interpreted by a single radiologist. Third, the sample size, although sufficient for the study design, limits the generalizability of the findings to broader populations. Additionally, this was a retrospective study, and further prospective studies are needed to confirm these results and evaluate the impact of different MRI protocols on diagnostic performance. Lastly, the exclusion of patients who had undergone neoadjuvant chemotherapy may limit the applicability of the findings to more advanced cases of endometrial cancer.

In conclusion, this study demonstrates that T2W, DWI, and DCE MRI sequences all have high accuracy in assessing myometrial invasion in endometrial cancer. Although the differences in performance were not statistically significant, T2W showed a slight advantage due to its superior anatomical detail and ability to assess the tumor in multiple planes. DWI also performed well, providing valuable functional information. In cases with complicating factors such as fibroids or adenomyosis, combining T2W and DWI is recommended to enhance accuracy and reduce the likelihood of misinterpretation. Further studies with larger sample sizes and 3T MRI systems are required to confirm and strengthen these findings.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Ferritin and Cardiac Electrophysiology in End-Stage Renal Disease: Evaluating the Impact of Index of Cardio-Electrophysiological Balance

Son Dönem Böbrek Yetersizliğinde Ferritin ve Kardiyak Elektrofizyoloji: Kardiyo-Elektrofizyolojik Denge İndeksinin Etkisinin Değerlendirilmesi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1595243
Geliş Tarihi | Received: 02.12.2024
Kabul Tarihi | Accepted: 11.01.2025
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Çoksevim M, Kertmen Ö, Yıldırım U, Türkmen E. Ferritin and Cardiac Electrophysiology in End-Stage Renal Disease: Evaluating the Impact of Index of Cardio-Electrophysiological Balance. Hitit Medical Journal 2025;7(1):37-44. https://doi.org/10.52827/hititmedj.1595243

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 27/11/2024 tarihinde Ondokuz Mayıs Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2024/511.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: AA Tasarım: AA Veri Toplama/Veri İşleme: AA, AAP Veri Analizi: AA Makalenin Hazırlanması: AA, AAP
Hasta Onamı: Çalışma retrospektif bir çalışma olarak dizayn edildiğinden çalışma için bilgilendirilmiş onam formuna gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from Ondokuz Mayıs University Clinical Research Ethics Committee on 27/11/2024. Decision no: 2024/511.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: AA Design: AA Data Collection/Data Processing: AA, AAP Data Analysis: AA Manuscript Preparation: AA, AAP
Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.
Financial Disclosure: There are no financial funds for this article.

Ferritin and Cardiac Electrophysiology in End-Stage Renal Disease: Evaluating the Impact of Index of Cardio-Electrophysiological Balance

ABSTRACT

Objective: Ferritin is a critical protein involved in iron storage and functions as an acute-phase reactant, playing a significant role in chronic inflammation and the pathogenesis of cardiovascular diseases. Elevated ferritin levels in end-stage renal disease patients undergoing hemodialysis may influence cardiac electrophysiological parameters, such as the corrected index of cardio-electrophysiological balance, a marker of proarrhythmic risk. This study aimed to investigate the association between ferritin levels and the corrected index of cardio-electrophysiological balance in patients with end-stage renal disease undergoing hemodialysis.

Material and Method: This retrospective cross-sectional study included 438 patients with end-stage renal disease undergoing hemodialysis, categorized into two groups according to their ferritin levels: Group 1 (≥1000 ng/mL, n=254) and Group 2 (≤200 ng/mL, n=184). Demographic, biochemical, and electrocardiographic data, including corrected index of cardio-electrophysiological balance, were analyzed. The correlation between ferritin levels and the corrected index of cardio-electrophysiological balance was assessed.

Results: The index of cardio-electrophysiological balance was significantly higher in Group 1 compared to Group 2 (5.1 vs. 4.9, *p=0.003*). A moderate positive correlation between ferritin levels and the index of cardio-electrophysiological balance was identified (r=0.326, *p<0.005*). While significant differences were observed in heart rate, QRS duration, and PR intervals between the groups, other electrocardiographic parameters, such as Tp-e and QT intervals, did not show significant differences. The logistic regression analysis identified gender and ferritin levels as significant predictors of elevated iCEBc (≥4.5) (Ferritin odds ratio of 1.08 (95% CI: 1.03–1.12, *p<0.005*).

Conclusion: Elevated ferritin levels in end-stage renal disease patients undergoing hemodialysis are associated with an increased corrected index of cardio-electrophysiological balance, reflecting heightened proarrhythmic risk. These findings underscore the importance of ferritin as a potential marker for arrhythmia risk assessment in this population. Further research is warranted to explore strategies for mitigating cardiovascular risks associated with iron metabolism dysregulation.

Keywords: End-stage renal disease, ferritin, hemodialysis, Index of Cardio-Electrophysiological Balance.

ÖZET

Amaç: Ferritin, demir depolanmasında anahtar bir protein olup, aynı zamanda kronik inflamasyon ve kardiyovasküler hastalıklarla ilişkili bir akut faz reaktanıdır. Hemodiyaliz uygulanan son dönem böbrek yetmezliği hastalarında artan ferritin seviyelerinin, proaritmik riski yansıtan kardiyo-elektrofizyolojik denge indeksi gibi elektrokardiyografik parametreleri etkileyebileceği düşünülmektedir. Bu çalışma, hemodiyaliz alan son dönem böbrek yetersizliği hastalarında ferritin seviyeleri ile kardiyo-elektrofizyolojik denge indeksi arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif, kesitsel çalışmada, hemodiyaliz uygulanan 438 son dönem böbrek yetersizliği hastası yer almıştır. Hastalar ferritin seviyelerine göre iki gruba ayrılmıştır: Grup 1 (≥1000 ng/mL, n=254) ve Grup 2 (≤200 ng/mL, n=184). Demografik, biyokimyasal ve elektrokardiyografik veriler (kardiyo-elektrofizyolojik denge indeksi dahil) analiz edilmiştir. Ferritin seviyeleri ile kardiyo-elektrofizyolojik denge indeksi arasındaki ilişki değerlendirilmiştir.

Bulgular: Kardiyo-elektrofizyolojik denge indeksi Grup 1'de Grup 2'ye kıyasla anlamlı derecede yüksek saptandı (5.1'e karşı 4.9, *p=0.003*). Ferritin düzeyleri ile kardiyo-elektrofizyolojik denge indeksi arasında orta düzeyde pozitif bir korelasyon tespit edilmiştir (r=0.326, *p<0.005*). Gruplar arasında kalp hızı, QRS süresi ve PR aralıklarında anlamlı farklılıklar gözlenirken, Tp-e ve QT aralıkları gibi diğer elektrokardiyografik parametreler anlamlı farklılıklar göstermemiştir. Lojistik regresyon analizi, cinsiyet ve ferritin düzeylerini yüksek iCEBc (≥4,5) için anlamlı öngörücüler olarak tanımlamıştır (Ferritin odds ratio 1,08 (%95 CI: 1,03-1,12, *p<0.005*).

Sonuç: Hemodiyaliz uygulanan son dönem böbrek yetersizliği hastalarında yüksek ferritin seviyeleri, proaritmik riski yansıtan kardiyo-elektrofizyolojik denge indeksi ile ilişkilendirilmiştir. Bu bulgular, ferritinin bu popülasyonda aritmi riski değerlendirmesinde potansiyel bir belirteç olarak önemini vurgulamaktadır. Çalışmamız ile demir metabolizmasının düzensizliği ile ilişkili kardiyovasküler riskleri azaltmaya yönelik stratejilerin araştırılması gerektiği sonucuna varılmıştır.

Anahtar Sözcükler: Ferritin, hemodiyaliz, Kardiyo-Elektrofizyolojik Denge İndeksi, Son dönem böbrek hastalığı.

Introduction

Ferritin is a protein essential for the storage and regulation of iron homeostasis, functioning at both intracellular and extracellular levels (1). Additionally, as an acute-phase reactant, elevated ferritin levels have been associated with chronic inflammation, metabolic disorders, chronic kidney failure, and cardiovascular diseases (2-6).

Elevated ferritin levels are frequently observed in individuals with end-stage renal disease (ESRD). Hemodialysis, a primary treatment for these patients, can further complicate iron regulation, contributing to elevated ferritin levels (5).

Both elevated and reduced ferritin levels have been linked to a heightened risk of arrhythmias and mortality in diverse patient populations (6,7). Additionally, increased serum ferritin levels have been shown to cause changes in QTc dispersion, which is a well-recognized marker associated with a greater likelihood of ventricular arrhythmias and sudden cardiac death (8).

Electrocardiographic parameters, including the frontal QRS axis, QT interval, QRS duration, Tp-E interval, and the corrected index of cardio-electrophysiological balance (iCEBc), are considered valuable tools for assessing cardiac health and identifying arrhythmogenic conditions. Studies have identified the iCEBc, the Tp-E interval, and the frontal QRS axis as potential markers for ventricular arrhythmias, sudden cardiac death, and overall mortality in various patient populations. (9-12).
Given the high incidence of cardiovascular complications in patients with ESRD, understanding the role of ferritin levels and their effects on electrocardiographic parameters is critical for developing strategies aimed at improving clinical outcomes. In this context, this study aims to investigate the relationship between elevated ferritin levels and electrocardiographic parameters in patients with ESRD.

Material and Methods

Study Population

This cross-sectional, retrospective, single-center study included patients who presented to nephrology and cardiology outpatient clinics between January 1, 2023, and January 1, 2024, and were undergoing hemodialysis treatment due to ESRD. Patients were stratified into two groups according to their ferritin levels: Group 1 comprised individuals with ferritin levels ≥ 1000 ng/mL, while Group 2 included those with ferritin levels ≤ 200 ng/mL.

The study excluded patients presenting with the following conditions: acute infections, severe coronary artery disease, moderate or severe valvular heart disease, atrial fibrillation, malignancy, chronic autoimmune diseases, abnormal serum electrolyte levels, ferritin levels between 200 and 1000 ng/mL, heart failure (EF <40%), or the presence of complete or incomplete bundle branch blocks or pacemaker rhythm on the electrocardiogram (ECG). Additionally, patients receiving treatments that could influence ECG parameters such as antiarrhythmic drugs, selective serotonin reuptake inhibitors, antibiotics, antifungals, antipsychotics, and others were excluded from the study.

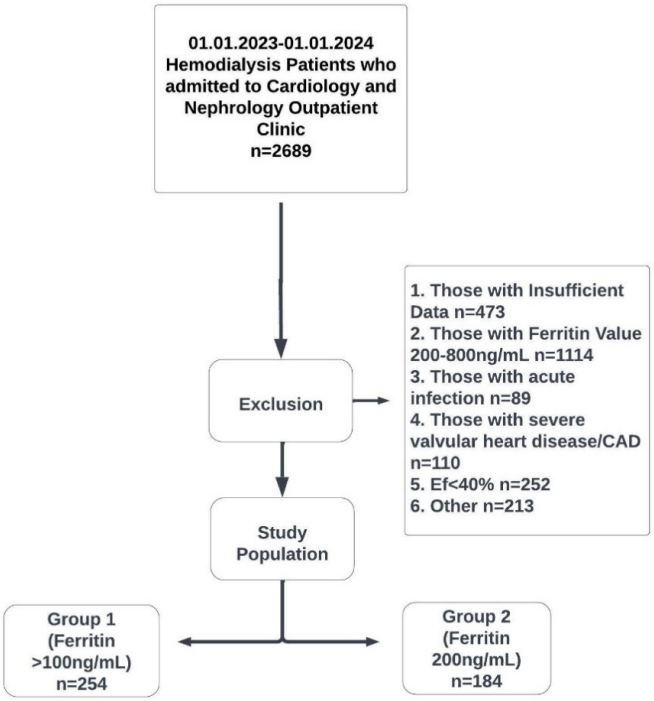
The study population consisted of 438 patients who met the inclusion criteria, with 254 participants in Group 1 (ferritin ≥ 1000 ng/mL) and 184 participants in Group 2 (ferritin ≤ 200 ng/mL).

Demographic data, as well as biochemical, hematological, and inflammatory parameters, were retrieved from the local database.

A 12-lead ECG was obtained for all participants.

The study design is illustrated in Figure I.

Figure I. Flow Chart of the Study Population



The research was conducted in accordance with the ethical principles outlined in the 1975 Declaration of Helsinki, and ethical approval was granted by the local ethics committee.

Electrocardiogram Assessment

Standard 12-lead ECGs were recorded using a device configured with a paper speed of 25 mm/s and an amplitude of 10 mm/mV. To reduce evaluation errors, a magnification tool was utilized. Measurements were conducted on leads V5 and DII. The ECG parameters analyzed included the T peak-to-end (Tp-e) interval, QRS duration, and QT interval.

The QT Interval: Measured from the onset of the QRS complex to the termination of the T wave.
The QTc Interval: QTc was calculated to account for heart rate variability using Bazett's formula:

$$QTc = \frac{QT}{\sqrt{R-R\ Interval}}$$

Tp-e Interval: The T peak-to-end (Tp-e) interval was measured from the peak of the T wave, identified as its highest point, to the end of the T wave, defined as the intersection of its descending limb with the baseline. In cases where a U wave was present, the end of the T wave was identified as the notch between the T and U waves. The Tp-e/QT and Tp-e/QTc ratios were subsequently calculated based on these measurements.

ICEB and ICEBc: The index of cardio-electrophysiological balance (ICEB) was calculated as QT/QRS, and the corrected index (ICEBc) as QTc/QRS, as described in the literature.

The coefficients of variation for interobserver measurements were 3.3% and intraobserver measurements were 4.0%.

Statistical analysis

The study data were analyzed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL). Descriptive statistics were reported as mean ± standard deviation, median (interquartile range), median (minimum–maximum), frequencies, and percentages. For categorical variables, statistical analysis was performed using Pearson's Chi-Square Test, Fisher's Exact Test, and McNemar's Test. The distribution normality of continuous variables was evaluated using both visual tools, such as histograms and probability plots, and statistical tests, including the Kolmogorov-Smirnov Test and the Shapiro-Wilk Test. For continuous variables with a normal distribution, comparisons between two independent groups were conducted using the Student's t-test. For variables that did not follow a normal distribution, the Mann-Whitney U Test was employed for comparisons between two groups. Correlations between variables were assessed using Spearman's Correlation Test. For the binary logistic regression analysis, an elevated iCEBc value was defined as ≥4.5 based on thresholds reported in the literature, and the analysis was conducted accordingly. A p-value of less than 0.05 was considered statistically significant.

Results

Baseline Demographic, Laboratory, and Echocardiographic Characteristics

The baseline demographic, laboratory, and echocardiographic characteristics of Group 1 (n = 254) and Group 2 (n = 184) are presented in Table I. Group 1 demonstrated distinct characteristics compared to Group 2. The median age was similar between the groups (59 years [48–68] in Group 1 vs. 60 years [48–70] in Group 2, *p=0.294*), with nearly identical proportions of females (48.4% in Group 1 vs. 48.9% in Group 2, *p=0.920*).

Table I. Baseline Demographic, Laboratory and Echocardiographic Findings of the Study Population

	Group 1 (n=254)	Group 2 (n=184)	p
Age, years	59 (48 - 68)	60 (48 - 70)	*0.294*
Female Sex, n (%)	123 (48.4%)	90 (48.9%)	*0.920*
HT, n (%)	192 (75.6%)	156 (84.8%)	***0.019***
DM, n (%)	84 (33.1%)	68 (37%)	*0.399*
HL, n (%)	55 (21.7%)	30 (16.3%)	*0.162*
CAD, n (%)	52 (20.5%)	38 (20.7%)	*0.963*
Rbc (milyon/nL)	3.6 (3.1 - 4.1)	3.7 (3.3 - 4.2)	***0.028***
Hb (g/dL)	10.6 (9.2 - 12)	10.8 (9.5 - 12.3)	*0.169*
Htc (%)	31.7 (27.7 - 36.6)	32.6 (29.2 - 36.9)	***0.032***
MCV (fL)	89.2 (85.1 - 94.4)	88.8 (84.5 - 93.8)	*0.317*
Na (mEq/L)	138.8 (136 - 141)	138.8 (136.8 - 140.5)	*0.638*
K (mEq/L)	4.8 (4.2 - 5.4)	4.8 (4.3 - 5.3)	*0.666*
Calcium (mg/dL)	9 (8.5 - 9.5)	9 (8.3 - 9.4)	*0.194*
Magnesium (mmol/L)	1 (0.8 - 1)	0.9 (0.8 - 0.9)	***0.006***
Fe (µg/dL)	75.4 (47.9 - 77.5)	56.5 (37.8 - 68.8)	***<0.005***
TIBC (µg/dL)	213.6 (194 - 213.6)	264.9 (237.7 - 284.6)	***<0.005***

Ferritin (ng/mL)	1465 (1211 - 2009.3)	116 (59 - 150)	***<0.005***
Ejection Fraction	55 (55 - 60)	54 (54 - 60)	*0.124*

Quantitative variables were specified as medians (Q1–Q3). Categorical variables were shown as numbers and percentage values.Ht: Hypertension; DM: Diabetus Mellitus; HL: Hyperlipidaemia; CAD: Coronary artery disease; Rbc: Red blood cell ; Hb: haemoglobin; Htc: haematocrit; MCV: Mean Corpuscular Volume; Na:Sodyum; K: Potassium; Cl: Clorur; Fe: İron; TIBC: Total iron binding capacity.

Laboratory values for Group 1 showed unique features. Iron levels (75.4 µg/dL [47.9–77.5]) were markedly higher in Group 1 compared to Group 2 (56.5 µg/dL [37.8–68.8], *p<0.005*), while total iron-binding capacity (TIBC) was significantly lower in Group 1 (213.6 µg/dL [194–213.6] vs. 264.9 µg/dL [237.7–284.6], *p<0.005*).

Red blood cell (RBC) counts and hematocrit levels were slightly lower in Group 1 (RBC: 3.6 [3.1–4.1] vs. 3.7 [3.3–4.2], *p=0.028*; hematocrit: 31.7% [27.7–36.6] vs. 32.6% [29.2–36.9], p=0.032). Other hematological and electrolyte parameters, including hemoglobin, sodium, potassium, calcium, and magnesium, did not differ significantly between groups.

Table II. Electrocardiographic Features of The Study Population

	Group 1 (n=254)	**Group 2 (n=184)**	***p***
Heart Rate, bpm	81.5 (70.8 - 92)	78 (68.3 - 89)	***0.026***
PR İnterval, ms	146 (130 - 166.5)	154 (138 - 172)	***0.012***
QRS Duration,ms	86 (80 - 96)	88 (82 - 95.8)	***0.028***
QT Interval,ms	382 (354 - 412)	386 (362.5 - 407.8)	*0.247*
cQT Interval, ms	442 (425.8 - 461)	436.5 (419 - 462.8)	*0.123*
Frontal QRS-T Angle (°)	40.5 (19.8 - 90.5)	36.5 (15.3 - 86)	*0.252*
Tp-e, ms	71 (60 - 80)	70 (60 - 80)	*0.402*
Tp-e/QT Ratio	0.2 (0.2 - 0.2)	0.2 (0.2 - 0.2)	*0.257*
Tp-e/QTc Ratio	0.2 (0.1 - 0.2)	0.2 (0.1 - 0.2)	*0.727*
iCEB (QT/QRS)	4.4 (4 - 4.8)	4.4 (4 - 4.7)	*0.305*
iCEBc (QTc/QRS)	5.1 (4.6 - 5.6)	4.9 (4.5 - 5.4)	***0.003***

Quantitative variables were specified as medians (Q1–Q3). QTc: Corrected QT interval; Tp-e:T wave peak-to-end; ICEB: index of cardioelectrophysiological balance; ICEBc: corrected ICEB

The logistic regression analysis identified gender and ferritin levels as significant predictors of elevated iCEBc (≥4.5). Ferritin levels had an odds ratio (OR) of 1.08 (95% CI: 1.03–1.12, *p<0.005*), indicating that each unit increase in ferritin was associated with an 8% increase in the likelihood of having an iCEBc ≥4.5. Other variables, including age, hemoglobin, diabetes, hypertension, hyperlipidemia, ejection fraction, magnesium, and iron levels, were not statistically significant predictors in the model (*p>0.05*).

Table III. Binary Logistic Regression Analysis of Factors Influencing the iCEBc ≥4.5

	OR (%95CI)	***p***
Gender	0,519 (0,31 - 0,87)	***0.013***
Age	0,994 (0,976 - 1,013)	*0.537*
Hemoglobin	0,985 (0,875 - 1,108)	*0.797*
Diabetes Mellitus	0,786 (0,449 - 1,378)	*0.401*
Hypertension	1,43 (0,718 - 2,851)	*0.309*
Hyperlipidemia	1,031 (0,542 - 1,961)	*0.927*
Ejection Fraction	1,022 (0,981 - 1,064)	*0.302*
Ferritin	1,08 (1,03-1,12)	***0.000***
Magnesium	1,622 (0,415 - 6,341)	*0.487*
Iron Level	0,999 (0,992 - 1,006)	*0.769*

Cox & Snell R Square=0.079; Nagelkerke R Square= 0.124; Accuracy= 0,799. iCEBc:Corrected index of Cardio-Electrophysiological Balance

Electrocardiographic Characteristics

The electrocardiographic features Group 1, presented in Table II, reveal some significant differences compared to Group 2. Group 1 had a higher median heart rate (81.5 bpm [70.8–92]) compared to Group 2 (78 bpm [68.3–89], *p=0.026*). The PR interval was shorter in Group 1 (146 ms [130–166.5] vs. 154 ms [138–172], *p=0.012*), and the QRS duration was also slightly shorter (86 ms [80–96] vs. 88 ms [82–95.8], *p=0.028*).

The corrected index of cardioelectrophysiological balance (iCEBc) was higher in Group 1 (5.1 [4.6–5.6]) compared to Group 2 (4.9 [4.5–5.4], *p=0.003*). No significant differences were noted in other electrocardiographic parameters, including QT interval, corrected QT (QTc) interval, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

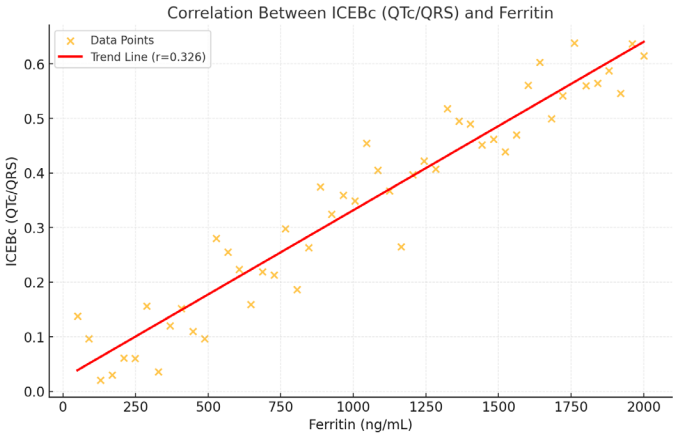
Correlation Analysis of ICEBc and Ferritin

The correlation analysis, summarized in Table III, revealed a statistically significant moderate positive correlation between iCEBc and ferritin levels in Group 1 (*r=0.326, p<0.005*). This indicates that higher ferritin levels in Group 1 are associated with elevated iCEBc values. (Figure II).

In summary Group 1 exhibited unique characteristics compared to Group 2, including higher ferritin and iron levels, lower TIBC, and higher iCEBc. These findings suggest a distinct profile of iron metabolism and cardiac electrophysiological properties in Group 1. The significant moderate correlation between ferritin

and iCEBc further highlights the potential interplay between iron storage and cardiac function.

Figure II. Correlation Between iCEBc and Ferritin



Discussion

To the best of our knowledge, this study is the first to provide evidence demonstrating an increase in the iCEBc in ESRD patients undergoing HD with ferritin levels >1000 ng/mL. A moderate correlation between iCEBc and ferritin levels was also identified. Serum iron levels significantly effect ECG parameters and are linked to proarrhythmic effects through various mechanisms (13). Iron overload has been shown to enhance the production of reactive oxygen species and depolarize mitochondrial membrane potential, thereby initiating calcium wave generation and promoting arrhythmogenesis (14). Conversely, low iron levels are also associated with arrhythmia risks, including prolonged QT and Tp-e intervals, which may increase the susceptibility to ventricular arrhythmias (15). These findings highlight the U-shaped relationship of serum iron levels with cardiac risk, where both low and high levels contribute to arrhythmic vulnerability (16). In our study, serum iron levels were observed to be significantly elevated in Group 1. Collectively, these findings underscore the importance of individualized iron management to mitigate cardiovascular and proarrhythmic risks associated with serum iron levels especially in patients with ESRD.

Serum ferritin is a key indicator of iron storage in the body (1). Furthermore, ferritin, in conjunction with transferrin and its' receptors, serves as an acute-phase reactant and is a component of the protein family involved in cellular defense against oxidative stress and inflammation. The H-ferritin gene is activated through the antioxidant-responsive element in response to oxidative stress and proinflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (17). Consequently, inflammatory conditions such as chronic diseases and cancer can naturally influence serum iron and ferritin levels (1).

High ferritin levels in patients with chronic cardiovascular disease have been associated with worse outcomes and increased mortality (7). Kuragano et al. identified hyperferritinemia described as serum ferritin >100 ng/mL as a significant risk factor for cardiovascular disease, hospitalization, and mortality in their study which was published at 2014 included 1,086 Japanese HD patients (18). Similarly, in a 2020 study, HD patients with high ferritin levels and low transferrin saturation—suggesting inadequate iron utilization for erythropoiesis—were found to have a higher risk of death and cardiovascular disease (4). In another study, Ahmed et al. demonstrated the association between high serum ferritin levels (≥800 µg/L) and left ventricular hypertrophy in HD patients (19). Based on these findings, we categorized our study population of ESRD patients receiving HD into a hyperferritinemia group (ferritin >1000 ng/mL) and a control group (ferritin <200 ng/mL). We believe that exploring the relationship between ferritin levels and electrocardiographically validated parameters can shed light on the evaluation of cardiovascular outcomes in HD patients.

In this context, iCEBc serves as a non-invasive parameter that offers insights into the depolarization and repolarization phases of the cardiac action potential, thereby reflecting the ventricular proarrhythmic risk (20). Although there are relatively fewer studies on iCEBc compared to other markers, it has been suggested to predict cardiac proarrhythmic risk more effectively than parameters such as Tp-e interval, Tp-e/QT ratio, and QT interval, which focus solely on repolarization (20,21).

iCEBc has emerged as a superior biomarker for identifying arrhythmogenic conditions compared to the QTc. Unlike QTc, which has limited sensitivity and specificity for arrhythmic risk, iCEBc provides a balanced measure of ventricular depolarization and repolarization, offering enhanced predictive value for

arrhythmias, including life-threatening ventricular fibrillation (22). Recent studies affirm that iCEBc correlates strongly with adverse cardiac outcomes and mortality, emphasizing its clinical significance in risk stratification and its potential application in diverse patient populations (23). These findings solidify iCEBc as a pivotal tool in cardiology for non-invasive arrhythmic risk assessment.

Yucetas et al. reported significantly higher iCEBc values in patients with subarachnoid hemorrhage, highlighting the proarrhythmic risk in this group (21). Similarly, Kaya et al. observed elevated iCEBc levels in patients with tinnitus, emphasizing its relevance to arrhythmogenic risk (24). Additionally Nafakhi et al. found increased pericardial fat volume in patients with elevated iCEBc levels, suggesting a higher cardiovascular disease risk in these patients (25). Sivri et al. reported a rise in iCEBc levels in ESRD patients post-dialysis compared to pre-dialysis, underlining the proarrhythmic state in this population. In our study, we demonstrated that in ESRD patients undergoing HD, who are already at high cardiovascular risk, elevated ferritin levels are associated with a moderate increase in arrhythmic risk as reflected by higher iCEBc values. This highlights the potential importance of ferritin as a marker for assessing proarrhythmic risk in this vulnerable population.

This study has several limitations that should be acknowledged. First, its retrospective, single-center design restricts the generalizability of the findings to wider populations. Second, there is the potential influence of confounders. To address this, we conducted a binary logistic regression analysis to adjust for age, gender, and other cardiovascular disease risk factors. However, even after these adjustments, the model accounted for only a modest proportion of the variation (7.9% to 12.4%) and demonstrated moderate predictive accuracy (79.9%), suggesting that additional unmeasured factors might contribute to iCEBc variability. Third, although we utilized standard methodologies for ECG measurements, interobserver and intraobserver variability could introduce minor measurement errors. Fourth, significant limitation of our study, is the lack of direct assessment of cardiovascular mortality and major cardiovascular adverse events. This omission reflects the inherent constraints of the retrospective design and limits our ability to explore the full clinical implications of iCEBc in predicting these outcomes. Lastly, this study focused only on ferritin and iCEBc without exploring other biomarkers or cardiac parameters that might provide additional insights into arrhythmic risks in ESRD patients. Future studies with a prospective design, larger sample sizes, and a broader scope of analysis are needed to validate and expand upon these findings.

Conclusion

This study revealed a significant increase in the iCEBc among patients with ESRD undergoing HD who exhibited elevated ferritin levels (>1000 ng/mL). Additionally, a moderate correlation between ferritin levels and iCEBc was identified. These findings suggest that elevated ferritin levels, commonly observed in ESRD patients, may contribute to an increased arrhythmic risk, as reflected by higher iCEBc values. Given the high cardiovascular risk in this population, our results emphasize the potential role of ferritin as a marker for assessing proarrhythmic risks and underline the importance of further investigation into strategies to mitigate these risks.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

The Diagnostic Accuracy of V/P Scintigraphy in Pulmonary Embolism and Superiority of V/P SPECT to V/P Planar Scintigraphy

Pulmoner Embolizmde V/P Sintigrafisinin Tanısal Doğruluğu ve V/P SPECT'in V/P Planar Sintigrafiye Üstünlüğü

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1553149
Geliş Tarihi | Received: 21.09.2024
Kabul Tarihi | Accepted: 05.02.2025
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Demirtaş Şenlik S, Uçmak G, Demirel BB, et al. The Diagnostic Accuracy of V/P Scintigraphy in Pulmonary Embolism and Superiority of V/P SPECT to V/P Planar Scintigraphy. Hitit Medical Journal 2025;7(1):45-52. https://doi.org/10.52827/hititmedj.1553149

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Bu retrospektif çalışma Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi Eğitim Planlama ve Koordinasyon Kurulu'ndan onay almıştır (No: 2014/360, Tarih: 11.09.2014)
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: SDŞ, GU, BBD Tasarım: SDŞ, GU, BBD Veri Toplama/Veri İşleme: SDŞ, HE, İK, AKF, FG Veri Analizi: BBD Makalenin Hazırlanması: SDŞ, GU, BBD, HE.
Hasta Onamı: Çalışma retrospektif bir çalışma olarak dizayn edildiğinden çalışma için bilgilendirilmiş onam formuna gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: This retrospective study received approval from the Education Planning and Coordination Committee of Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (No: 2014/360, Date: 11.09.2014)
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: SDŞ, GU, BBD Design: SDŞ, GU, BBD Data Collection/Data Processing: SDŞ, HE, İK, AKF, FG Data Analysis: BBD Manuscript Preparation: SDŞ, GU, BBD, HE
Informed Consent: Since the study was designed as a retrospective study, obtaining an informed consent form was not required.
Financial Disclosure: There are no financial funds for this article.

The Diagnostic Accuracy of V/P Scintigraphy in Pulmonary Embolism and Superiority of V/P SPECT to V/P Planar Scintigraphy

ABSTRACT

Objective: The aim of this retrospective study is to investigate the diagnostic accuracy of planar V/P scintigraphy and V/P single-photon emission computed tomography (SPECT) in patients who referred to our clinic for V/P scintigraphy with prediagnosis of pulmonary embolism (PE), as well as to investigate the contribution of V/P SPECT technique to planar V/P technique.

Material and Method: The records of 204 patients, who were preliminarily diagnosed with PE within 1 year, were retrospectively reviewed. In our investigation of the diagnostic accuracy of V/P scintigraphy in for PE, we excluded three patients who only underwent perfusion scintigraphy and 20 patients whose final diagnoses could not be confirmed. This left a total of 181 patients included in the statistical analysis. Furthermore, we evaluated the contribution of SPECT to planar imaging in 48 patients, for whom V/P Scintigraphy were reported as positive and whose final diagnoses confirmed PE.

Results: The sensitivity, specificity, negative predictive value, positive predictive value, and accuracy rate of V/P SPECT were calculated as 98%, 94.7%, 99.2%, 87.3%, and 95.6%, respectively. For planar scintigraphy, they were found to be 71.4%, 95.4%, 90%, 85.3%, and 88.9%, respectively. In SPECT, 13 (27.1%) patients who were not compatible with pulmonary embolism (PE) on planar imaging were found to have findings consistent with PE. In nine patients (18.8%), additional defects not observed on planar imaging were identified. Although the goodness of fit with the final diagnosis of both methods was statistically significant, SPECT (95.6%) performed better than planar (88.9%) imaging.

Conclusion: Consistent with previous studies, it was found that while both imaging methods were successful, SPECT demonstrated higher diagnostic accuracy than planar scintigraphy in diagnosing PE. Therefore, it can be hypothesized that V/P scintigraphy can be safely deemed the first-choice in the diagnosis of PE.

Keywords: Pulmonary Embolism, V-P Scintigraphy, SPECT.

ÖZET

Amaç: Bu çalışmada pulmoner embolizm (PE) tanısında, ventilasyon/perfüzyon (V/P) planar sintigrafinin ve tek foton emisyonlu bilgisayarlı tomografi (SPECT)'nin tanısal doğruluğunu ve SPECT'in planar görüntülemeye katkısını araştırmak amaçlandı.

Gereç ve Yöntem: 1 yıl boyunca Pulmoner Embolizm (PE) ön tanısı ile başvuran 204 hastanın kayıtları retrospektif olarak incelendi. Pulmoner embolizmde V/P sintigrafinin tanısal doğruluğu araştırılırken, sadece perfüzyon sintigrafisi yapılan 3 hasta ve son tanısına ulaşılamayan 20 hasta dışlandı ve toplam 181 hasta istatistiksel analiz çalışmasına dahil edildi. SPECT'in planar görüntülemeye katkısı, V/P SPECT' in PE ile uyumlu olarak raporlandığı ve son tanısı PE olan 48 hasta değerlendirilerek yapıldı.

Bulgular: 181 hasta göz önüne alındığında; V/P SPECT'in sensitivitesi %98 (48/49), özgüllüğü %94,7 (125/132), negatif öngörü değeri %99,2, pozitif öngörü değeri %87,3 ve doğruluk oranı %95,6 olarak hesaplandı. Planar sintigrafi için sırasıyla 71.4%, 95.4%, 90% (126/140), 85.3 % (35/41) ve 88.9% olarak hesaplandı. SPECT görüntüleme, planar V/P sintigrafi ile PE tanısı konulamayan 13 hastada (%27,1) PE ile uyumlu sonuçların raporlanmasını sağladı. V/P SPECT ile 9 hastada takip sintigrafisinde önemli olabilecek ek lezyonlar (%18,8) tespit edildi. Her iki yöntemin kesin tanı ile uyumunun istatistiksel olarak anlamlı olduğu gözlemlendi, ancak SPECT bulgularının kesin tanı ile uyumunun (%95.6) planar bulguların kesin tanı ile uyumundan (%88.9) daha iyi olduğu görüldü.

Sonuç: Önceki çalışmalarla benzer şekilde, V/P sintigrafide her iki görüntüleme yöntemi de başarılı olmasına rağmen, SPECT'in planar görüntülemeye önemli ölçüde katkıda bulunduğu ve SPECT'in PE tanısında yüksek hassasiyet, özgüllük ve doğruluk sağladığı bulundu.

Anahtar Sözcükler: Pulmoner Emboli, V/P Planar Sintigrafi, SPECT.

Introduction

Pulmonary embolism (PE) is a prevalent obstructive vascular disease with an annual incidence of approximately 39–115 per 100,000. Due to the high mortality rate in untreated cases, immediate diagnosis and treatment are crucial (1,2,3). Thus, it is essential to rapidly and accurately diagnose PE to plan treatment successfully. Lung ventilation/perfusion (V/P) scintigraphy is a non-invasive, fast diagnostic procedure with low radiation exposure, making it one of the preferred methods for diagnosing PE. This process is based on identifying areas with impaired pulmonary blood supply but preserved alveolar ventilation (mismatch defects) (4).

Combined V/P scintigraphy enhances the diagnostic specificity of PE and can provide further information on alternate diagnoses such as pneumonia, chronic obstructive pulmonary disease (COPD), and heart failure. In selected cases such as pregnant patients and suspected instances of massive embolism, it is possible to use only perfusion scintigraphy (5). Moreover, studies have indicated that both V/P planar imaging, and V/P single-photon emission computed tomography (SPECT) are highly effective for diagnosing chronic thromboembolic pulmonary hypertension (CTEPH). Additionally, perfusion SPECT in conjunction with low-dose computed tomography (CT) is a reliable alternative method for those patients for whom ventilation imaging is unsuitable (6). During the COVID-19 pandemic, using only perfusion scintigraphy without ventilation is more suitable as ventilation scintigraphy might escalate the risk of infection spread through aerosol leakage. Lung X-ray imaging or SPECT/CT is preferable to evaluate lung parenchyma in cases where ventilation scintigraphy may not be performed (7,8).

SPECT is a scanning method utilized in nuclear medicine. Images are acquired by rotating the gamma camera 360 degrees around the patient, producing three-dimensional data. The preparation of the patient, along with the injection and inhalation of radiopharmaceuticals, mirrors the procedures used in planar imaging. SPECT is a readily applicable technique aimed at enhancing diagnostic accuracy in planar V/P without necessitating an additional radiopharmaceutical injection. Studies affirm its superior positive and negative predictive value, as well as its objectivity in assessing PE (9). Occasionally, SPECT may be fused with low-dose CT to perform the hybrid imaging technique, SPECT/CT (10).

The objective of this retrospective study was to evaluate the diagnostic accuracy of planar V/P scintigraphy and V/P SPECT in patients referred to out clinic for V/P scintigraphy with suspected PE. Additionally, we aimed to analyze the added diagnostic value provided by the V/P SPECT technique compared to the planar V/P technique.

Material and Method

This retrospective study received approval from the Education Planning and Coordination Committee of Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (No: 2014/360, Date: 11.09.2014), and the need for informed consent was thus waived.

Two hundred and four patients suspected of having PE, who were referred to our clinic for V/P scintigraphy over 1 year (2014-2015), were considered for the current study. A retrospective review of their records was conducted. Three patients who underwent only perfusion scintigraphy and another 20 patients for whom final diagnostic information was unavailable, were excluded from the study. Consequently, a total of 181 patients were included in the statistical evaluation.

V/P Scintigraphy: Perfusion imaging was carried out following the intravenous injection of 100–120 MBq Technetium-99m macroaggregated albumin (99mTc-MAA) while the patient was under the camera in a supine position. The average particle number applied was between 300,000–500,000 in patients with normal Pulmonary Artery Pressure (PAP). However, in 23 patients with increased PAP, the particle number was halved. Ventilation Scintigraphy utilized Technegas, with ultrafine aerosol prepared using specialized heating devices (Cyclomedia tecnegasplus, Australia). The system's ventilation set was used for inhaling a radiotracer, established by positioning double 550 MBq technetium in carbon graphite. V/P imaging was completed using general-purpose low-energy parallel hole collimators. Imaging was conducted after 3–5 cycles of respiration, without delay.

V/P imaging was performed using general-

purpose low-energy parallel hole collimators and double-headed gamma detector cameras (Siemens E-cam, Germany). The planar imaging utilized a 256 × 256 matrix with a 360-degree rotation angle, taking eight views from four projections: anterior-posterior, right anterior oblique-left posterior oblique, right lateral-left lateral, right posterior oblique-left anterior oblique. Each projection captured 500,000 counts. The SPECT study was conducted with a 64 × 64 matrix and a 360-degree rotation angle in 32 steps (one step every 10s in ventilation scintigraphy and one step every 5s in perfusion scintigraphy). Images were reconstructed using the back-projection technique. A 'Butterworth filter' was employed for filtering the images, which were then evaluated after processing in workstations (Xeleris-GE).

In patients who underwent the 1-day protocol, ventilation scintigraphy was performed first, followed by perfusion scintigraphy without changing the patient's position. For the 2-day protocol, perfusion scintigraphy was carried out on the first day, and ventilation scintigraphy was performed on the following day. There are no specific selection criteria for either the 1-day or 2-day protocols. The 1-day protocol requires a longer scanning time, so it was preferred when the patient's general condition was stable. For both protocols, planar imaging was conducted first, followed by SPECT imaging.

V/P Planar and V/P SPECT images were assessed as either positive or negative for the presence of PE, and non-diagnostic, in line with the main criteria recommended by the European Association of Nuclear Medicine (EANM) guidelines. The report was based on findings from the V/P SPECT (5).

Images exhibiting at least one segmentary or two subsegmentary mismatch defects on V/P scintigraphy were classified as being consistent with PE. A normal perfusion pattern, matched or reverse mismatch defects of any number and size, and mismatch defects that failed to align with the lobar-segmentary or subsegmentary pattern were documented as incompatible with PE. A variety of V/P anomalies that were not specific to any disease were reported as non-diagnostic or suspicious findings.

Therefore, like previous studies, we based our final diagnosis on clinical and laboratory findings, imaging results, treatment, and follow-up re-evaluation. Follow-ups were conducted 6–12 months post-diagnosis, using findings procured from the hospital database (clinical, laboratory, control V/P scintigraphy, and CT pulmonary angiography).

Statistical Analysis

The data gathered from V/P planar scintigraphy and SPECT findings were statistically analyzed for the detection of PE. The "Cochran's Q test" was used to determine if there was a correspondence between the diagnoses, while the significance of the distribution of the methods according to the categories of presence or absence of embolism was tested with the "pairwise comparisons" approach, and the final diagnosis. The compatibility of SPECT and planar methods with the final diagnosis was analyzed using the "chi-square" goodness of fit test. *p-values <0.01* were considered significant. The sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of both planar scintigraphy and SPECT were calculated. The contribution of SPECT to planar imaging was analyzed for the true positive patients (n = 48), these patients had positive V/P scintigraphy results and were diagnosed with PE.

Results

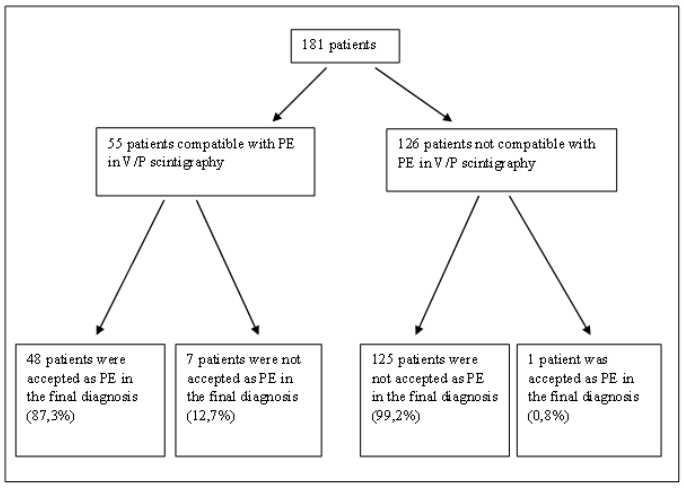
In the study, 181 patients were included, of which 130 were women and 51 were men, with a mean age of 60 ± 15.2 (age range: 19–88). The patients' reasons for seeking out a clinician, in order of frequency, were chest-back pain, shortness of breath, and more infrequently, a cough, palpitations, presyncope, and occasionally, a combination of these symptoms. The risk factors for PE in patients are shown in Table I. Analyses were conducted with the 181 patients for whom final diagnosis information was available (Figure l).

Findings suggestive of PE were detected in 43 patients via planar scintigraphy and in 59 patients via SPECT, whereas 158 patients were not accepted as having PE based on planar scintigraphy (with no defects, single sub-segmentary defects, or match/reverse mismatch defects), and 142 patients were excluded in the case of SPECT.

In 181 patients, SPECT imaging identified positive scintigraphic findings compatible with PE in 13

patients (27.1%) that were not detected by planar V/P scintigraphy alone. Furthermore, V/P SPECT allowed for clearer differentiation between suspicious defects in 8 patients (16.7%), and it revealed additional defects in 9 patients (18.8%) (Figure II).

Figure I. Final Diagnosis of the Patients According to the Results Obtained by Evaluating V/P Scintigraphy, PE: pulmonary embolism, V/P: ventilation/perfusion



According to the results from the Chi-square goodness of fit test, the correspondence between SPECT and the final diagnoses was 95.6% [(125 + 48) / 181], a significantly notable finding (χ2: 145.032; *p<0.01*). Similarly, the agreement between planar imaging and the final diagnoses was 88.9% [(126 + 35) / 181], and this result was also significant (χ2: 91.237; *p <0.01*). Although both methods' goodness of fit with the final diagnosis was statistically evident, the SPECT findings' concurrence with the final diagnosis (95.6%) was substantially higher than the final diagnosis concurrence with planar findings (88.9%) (*p=0.001*; Table I)

Table I. The Frequencies of Patients' Risk Factors for PE

Risk Factor	Incidence (n:181)
Deep vein thrombosis	12 (6.6%)
Previous pulmonary embolism	6 (3.3%)
Malignancy	39 (21.5%)
Chemotherapy/Radiotherapy	19 (10.5%)
Obesity	77 (42.5%)
Recent operation/immobilization	4 (2.2%)

Post-treatment control V/P scintigraphy was administered to 8 out of 48 patients being treated for embolism, and pulmonary CT angiography was administered to 4 patients. Of the 8 who underwent post-treatment V/P scintigraphy, 5 showed complete disappearance of the defects that were observed at the time of diagnosis, while in 2 patients, some defects regressed and others disappeared. There were new defects observed in 1 patient. Among the patients who underwent post-treatment CT angiography, no significant thrombus was observed in 3 patients, yet findings suggestive of a thrombus were still detected in 1 patient.

Table II. Comparison of V/P Planar and SPECT Results with Final Diagnosis

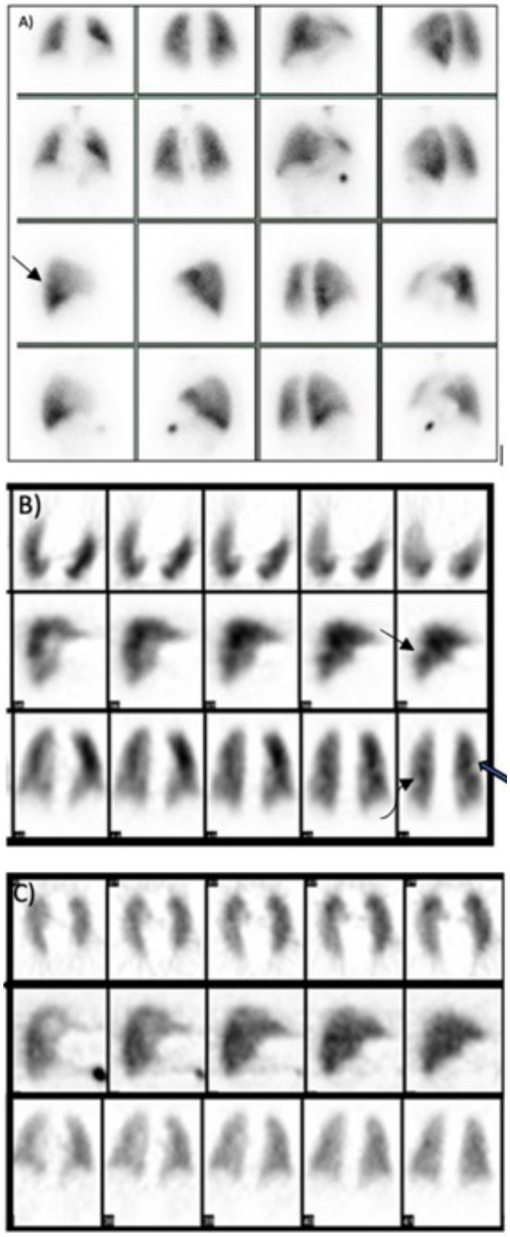
		Final Diagnosis (n:181)		
		Accepted as PE	Not accepted as PE	*p value*
Planar	With PE	35 (71.4%)	6 (4.5%)	*<0.01*
	Not with PE	14 (28.6%)	126 (95.5%)	
SPECT	With PE	48 (97.9%)	7 (5.3%)	*<0.01*
	Not with PE	1 (2.1%)	125 (94.7%)	

PE: pulmonary embolism, With PE: compatible with PE, Not with PE: not compatible with PE

During the follow-up, conducted 6–12 months post-treatment, clinical examination, imaging, and laboratory tests (CT angiography, V/P scintigraphy, D-dimer) indicated that symptoms had disappeared in 38 patients. Complaints were reduced in 6 patients, continued in 1 patient, and 3 patients died due to malignant-metastatic disease.

At the time of diagnosis, Pulmonary CT angiography was performed on 4 out of 7 patients who were considered to be deemed positive for PE in V/P SPECT (considered as false positive) but were not ultimately diagnosed with PE. In the Pulmonary CT angiography, the distal branches could not be evaluated in 3 patients, and the study was reported as suboptimal for 1 patient. In the follow-up examination, it was observed that the complaints of 5 patients persisted, while the complaints of 2 patients ceased. In 1 patient (considered a false negative), whose V/P scintigraphy was reported to be negative for PE, the final diagnosis indicated the presence of PE due to compelling clinical suspicion, taking into account the patient's age, symptoms, and existing malignancy. The treatment for PE was initiated and it was observed that the patient's complaints disappeared during follow-up.

Figure II. A 68-year-old female patient, followed up for breast cancer, presented to the chest diseases outpatient clinic with complaints of shortness of breath that started 1 day ago.
A) On the V/P planar images (The lines from top to bottom are as follows: sections of coronal perfusion, coronal ventilation, sagittal perfusion, sagittal ventilation), a subsegmental defect in the superior segment of the right lower lobe was observed, although unclearly (arrow). B) In the SPECT perfusion scan, perfusion defects were observed in the superior (arrow) and posterobasal segments (curved arrow) of the right lower lobe, as well as in the superior segment of the left lower lobe (thick arrow). C) In SPECT ventilation scan, ventilation was preserved in areas with perfusion defects (mismatch defects). These mismatch defects were reported as consistent with pulmonary embolism (PE). In the follow-up visit of the patient at 6 months after the initiation of treatment, it was found that her symptoms (the symptoms that lead to suspicion of pulmonary embolism) had disappeared.



Considering the patients for whom we could access the final diagnosis (n = 181); the sensitivity of V/P SPECT was calculated to be 98% (48/49), the specificity 94.7% (125/132), the NPV 99.2%, the PPV 87.3%, and the accuracy was 95.6%.

The sensitivity for planar scintigraphy was found to be 71.4% (35/49), specificity 95.4% (126/132), NPV 90% (126/140), PPV 85.3% (35/41), and accuracy 88.9%.

Discussion

Acute PE is a severe clinical presentation with a high mortality rate in untreated cases (1). Whereas the mortality rate for PE is approximately 25–30% without treatment, it can be reduced to 2–8% with proper and timely treatment. Pulmonary ventilation/perfusion (V/P) scintigraphy is frequently employed in diagnosing PE because of its non-invasive nature, ease of use, affordability, low radiation dosage, and high sensitivity (2).

This study demonstrated that V/P SPECT is highly reliable for the diagnosis of pulmonary embolism (PE), even without the inclusion of low-dose CT, providing evidence that V/P SPECT offers comparable diagnostic performance to SPECT/CT in detecting PE. Our findings highlight the utility of V/P SPECT as an effective and non-invasive imaging modality for PE diagnosis, aligning with previous studies that support its high sensitivity and specificity.

In a study published by Bajc et al. in 2008, 2328 patients who underwent V/P SPECT due to suspected PE were evaluated holistically. This approach, like our study, concluded that V/P SPECT had both a high negative and PPV (11).

Gutte et al. conducted a prospective study in 2010, comparing V/P planar and SPECT/CT imaging with 41 patients. The study reported that the sensitivity of V/P planar scintigraphy was 64%, with a specificity of 72%. Sensitivity for V/P SPECT/CT amounted to 100%, and specificity was 87%. Furthermore, V/P SPECT/CT demonstrated superior diagnostic accuracy, sensitivity, and specificity compared to Multidetector CT (MDCT) (12). The likelihood of a PE event following a negative MDCT of the pulmonary arteries is 1.5%, whereas the possibility of PE in follow-up after a negative V/P SPECT is at 0.4%

(13). Generally, MDCT is seen as a more efficient method for detecting larger and medium-sized emboli, while V/P SPECT might be more beneficial for lower-risk situations and smaller emboli (9). Although untreated subsegmental thrombi might not cause severe clinical issues, they can recur and give rise to chronic PE and pulmonary hypertension (14). Some studies suggest that a new generation of MDCT angiography, offering better spatial and temporal resolution, may be more sensitive than previous iterations in detecting subsegmental thrombi (14). Approximately 10–30% of patients cannot undergo CT angiography due to kidney diseases or contrast allergy. Moreover, V/P SPECT and V/P SPECT/CT expose patients to lower radiation doses in comparison to CT pulmonary angiography (14). According to the National Institute for Health and Care Excellence (NICE) guidelines, V/P scintigraphy was used as the first-choice in patients with a contrast allergy, renal insufficiency, and high radiation risk (15). For cases involving contrast allergy, pregnancy, and renal insufficiency – which are also mentioned in current guidelines – this imaging modality should be considered as the first-choice method.

In a retrospective study conducted by Gutte et al. and published in 2009, V/P SPECT/CT and MDCT were compared (9). Based on this study's results, Gutte et al. proposed that V/P SPECT, when combined with low-dose CT, could offer excellent diagnostic performance and thus be the first method of choice in the diagnosis of PE.

In our study, the sensitivity and specificity of V/P SPECT, even without low-dose CT, were as high as those reported in the SPECT/CT results of Gutte et al.'s study (9). The differences observed between the studies might be attributed to variations in study designs, the technical methods of scintigraphy used, and observer experiences.

In the 2019 EANM guidelines, V/P SPECT was considered the first-choice method for PE diagnosis, if available/applicable (10). An important advantage of V/P SPECT over planar imaging is the reduction of non-diagnostic/indeterminate results. In the study by Leblanc et al., 18 (3%) out of 584 patients, Bajc et al. reported 19 (1%) out of 2328 patients, and Lemb et al. reported 5 (0.5%) out of 991 patients as non-diagnostic when using V/P SPECT (10,16,17). A study conducted by Reinartz et al. in 2004 compared the V/P planar, SPECT imaging, and multi-spiral CT methods. They found that SPECT had the highest sensitivity, whereas CT had the highest specificity. The numbers of accurate diagnoses in the study population (n=83) were 67, 78, and 77 for the V/P planar, V/P SPECT, and CT methods, respectively. The study concluded that SPECT could replace the planar method (18). We found that SPECT is highly reliable for PE diagnosis, despite the absence of the CT component. However, the CT component would provide significant additional information regarding parenchymal pathologies, particularly in situations where ventilation scintigraphy is not preferred, like during the COVID-19 pandemic. A systematic review of perfusion-ventilation scans in COVID-19 patients concluded that SPECT/CT and perfusion scintigraphy combination could aid in mitigating diagnostic challenges associated with COVID-19 (19). The increased incidence of thromboembolic events and suspected pulmonary embolism during the COVID-19 pandemic has highlighted the valuable contribution of Perfusion SPECT-CT in the investigation of PE (20).

Our study has several limitations. First, this study is a retrospective study conducted at a single center. Another limitation is that not all patients could undergo pulmonary angiography, the gold standard test in diagnosing PE, due to its invasive nature and unfeasibility at times. Furthermore, not all patients received V/P scans during follow-up to assess treatment efficacy.

Conclusion

Both V/P planar scintigraphy and SPECT imaging were effective in diagnosing PE. However, SPECT provided greater diagnostic value than planar scintigraphy. Due to its low radiation exposure, suitability for use in pregnant women, low rate of non-diagnostic results, and high diagnostic performance, V/P scintigraphy combined with SPECT imaging should be an indispensable part of clinical practice.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Comorbidity Profile of Familial Mediterranean Fever Patients Varies by Treatments

Ailevi Akdeniz Ateşi Hastalarının Tedavilere Göre Değişen Komorbidite Profili

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1582847
Geliş Tarihi | Received: 11.11.2024
Kabul Tarihi | Accepted: 25.01.2025
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Kayacan Erdoğan E, Babaoğlu H, Coşkun Ş, et al. Comorbidity Profile of Familial Mediterranean Fever Patients Varies by Treatments. Hitit Medical Journal 2025;7(1):53-60. https://doi.org/10.52827/hititmedj.1582847

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma protokolü Ankara Bilkent Şehir 1 Nolu Hastanesi Etik Kurulu tarafından onaylandı (Tarih: 06/09/2023, Etik onay numarası: E1-23-3897).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: EKE, BA, HB Tasarım: EKE, BA, HB Veri Toplama/Veri İşleme: EKE, HB, ŞC, RKU, KO, SCG, EA, BÖU, HEK, PAD, ÖK, HA, BP, İD, YM, ŞE, AO, OK, BA Veri Analizi: EKE, BA, HB Makalenin Hazırlanması: EKE, HB, ŞC, RKU, KO, SCG, EA, BÖU, HEK, PAD, ÖK, HA, BP, İD, YM, ŞE, AO, OK, BA.
Hasta Onamı: Hastalardan onam alınmasına gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
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Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: The Ethics Committee of Ankara Bilkent Şehir Hospital No 1 approved the study protocol (Date:06/09/2023, Ethical approval number: E1-23-3897).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: EKE, BA, HB Design: EKE, BA, HB Data Collection/Data Processing: EKE, HB, ŞC, RKU, KO, SCG, EA, BÖU, HEK, PAD, ÖK, HA, BP, İD, YM, ŞE, AO, OK, BA Data Analysis: EKE, BA, HB Manuscript Preparation: EKE, HB, ŞC, RKU, KO, SCG, EA, BÖU, HEK, PAD, ÖK, HA, BP, İD, YM, ŞE, AO, OK, BA.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Comorbidity Profile of Familial Mediterranean Fever Patients Varies by Treatments

ABSTRACT

Objective: Comorbidities may have an impact on the patient's quality of life and even survival. Treatment resistance in Familial Mediterranean Fever (FMF) may indirectly indicate severe disease, with inflammation-related comorbidities increasing as severity rises. In the literature, there are no sufficient studies regarding comorbidities in FMF patients. In this study, we aimed to evaluate the comorbid conditions of patients according to FMF treatment steps.

Material and Method: We retrospectively reviewed 740 patients with FMF treated at our rheumatology clinic between May 2019 and March 2024. Patient characteristics, comorbidities, and FMF treatments of patients were evaluated. Patients were grouped according to their FMF treatment: coated colchicine, compressed colchicine, and IL-1 inhibition. Patients received treatments aligned with their disease activity, in accordance with current reimbursement guidelines.

Results: The mean age (SD) of FMF patients was 40.7 (13.3) and 62.4% were female. Of the 44.7% all patients had at least one comorbidity. The three most common comorbidities are hypertension (20%), hyperlipidemia (7%), and depression (6.8%). The initial coated colchicine treatment was changed in a total of 24.5% to compressed colchicine, further step up was done in 13.2% patients to IL-1 inhibition. Hypertension and chronic kidney disease were more common in patients under IL-1 inhibitor treatment.

Conclusion: Our retrospective analysis shows that FMF patients, especially those in the IL-1 inhibitor group, frequently experience comorbidities like hypertension, hyperlipidemia, and depression, even though these patients are younger, suggesting a potential link to severe disease. A comprehensive evaluation of comorbidities, especially in severe disease, is essential to prevent complications, and improve quality of life.

Keywords: Colchicine, comorbidity, Familial Mediterranean Fever, hypertension.

ÖZET

Amaç: Komorbiditelerin hastanın yaşam kalitesi ve hatta sağkalımı üzerinde etkisi olabilir. Ailevi Akdeniz Ateşi (AAA) hastalarında tedaviye direnç/başarısızlık, şiddetli hastalığın dolaylı bir göstergesi olabilir. AAA hastalık şiddeti arttıkça, inflamasyon ve hasara bağlı komorbiditeler de artabilir. Literatürde AAA hastalarında, özellikle de tedaviye dirençli gruptaki erişkin hastalarda komorbiditelere ilişkin yeterli çalışma bulunmamaktadır. Bu çalışmada, AAA tedavi basamaklarına göre hastaların komorbid durumlarının değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Mayıs 2019 ile Mart 2024 tarihleri arasında romatoloji kliniğimizde tedavi edilen 740 AAA hastası retrospektif olarak incelendi. Hastaların demografik özellikleri, komorbiditeleri, ailede AAA öyküsü ve AAA tedavileri değerlendirildi. Hastalar AAA tedavilerine göre kaplanmış kolşisin, sıkıştırılmış kolşisin ve IL-1 inhibitörü olmak üzere 3 gruba ayrıldı. Hastalar, mevcut geri ödeme kılavuzlarına uygun olarak hastalık aktiviteleri ile uyumlu tedaviler almıştır.

Bulgular: AAA hastalarının ortalama yaşı (SD) 40,7 (13,3) ve %62,4'ü kadındı. Hastaların %44,7'sinde en az bir komorbidite vardı. En sık görülen üç komorbidite hipertansiyon (%20), hiperlipidemi (%7) ve depresyondur (%6,8). Başlangıçtaki kaplanmış kolşisin tedavisi toplam %24,5 hastada sıkıştırılmış kolşisin olarak değiştirilmiş, %13,2 hastada ise IL-1 inhibisyonuna geçilmiştir. IL-1 inhibitörü tedavisi gören hastalarda hipertansiyon ve kronik böbrek hastalığı daha yaygındır.

Sonuç: Retrospektif analizimiz, AAA hastalarının, özellikle IL-1 inhibitörü grubundakilerin, daha genç olmalarına rağmen, hipertansiyon, hiperlipidemi ve depresyon gibi komorbiditeleri sıklıkla yaşadığını göstermektedir ve bu da şiddetli hastalık ve kronik inflamasyon arasında potansiyel bir bağlantı olduğunu düşündürmektedir. Özellikle şiddetli hastalığı olanlarda komorbiditelerin kapsamlı bir şekilde değerlendirilmesi, komplikasyonları önlemek ve yaşam kalitesini artırmak için gereklidir.

Anahtar Sözcükler: Ailevi akdeniz ateşi, hipertansiyon, kolşisin, komorbidite.

Introduction

Familial Mediterranean Fever (FMF) is an autoinflammatory disorder marked by recurrent episodes of fever and serositis (1). It is linked to mutations in the MEFV gene, following an autosomal recessive inheritance pattern, with common mutations including M680I, M694V, and V726A (2).

Colchicine is the primary treatment; however 5-15% of patients are resistant or intolerant to it (3). In patients resistant or intolerant to colchicine, IL-1 inhibitors are the next line of approved treatments. However, in specific cases, other treatments such as tumor necrosis factor inhibitors for those with chronic arthritis and IL-6 inhibitors for those with amyloidosis can be used (4,5). There are differing opinions on the use of IL-1 antagonists in FMF treatment, with some suggesting they can be administered either continuously or on-demand, depending on the patient's clinical presentation (6). Recent studies have investigated the efficacy of different colchicine preparations in FMF treatment (7). Currently, colchicine preparations are divided into compressed and coated (sugar coated). The greater effectiveness of compressed colchicine is attributed to its different pharmacokinetic properties compared to sugar coated tablets (8). Compressed colchicine also improved treatment response in patients who were resistant or intolerant to coated colchicine (9). These findings suggest that compressed colchicine tablets may be a useful treatment option for FMF patients prior to initiating biological agents, particularly for those experiencing side effects or an inadequate response to coated colchicine (7,9). In line with this data, according to Türkiye's reimbursement rules, FMF patients are initially treated with coated colchicine. If they exhibit resistance or intolerant to this form, they are then prescribed compressed colchicine. For patients whose disease remains uncontrolled (characterized by persistent inflammation or frequent attacks) after six months of compressed colchicine therapy, IL-1 inhibitors, such as anakinra and canakinumab, are added to the treatment regimen. However, despite the expanded treatment options in FMF, subclinical or chronic inflammation can be seen in 15-25% of FMF patients (10). These treatment steps can be considered as an indicator of disease severity.

All chronic inflammatory rheumatic diseases (CIRDs) are associated with an increased risk of comorbidities, such as cardiovascular diseases, malignancies, infections, gastrointestinal diseases, osteoporosis, and depression (11,12). However, data on FMF and comorbidities in the literature are limited. Comorbidities in FMF are mainly studied in pediatric patients and are categorized into three groups: inflammation-related, FMF associated, and incidental (13). In a study, 158 adult FMF patients were evaluated, and the frequency of non-FMF-associated comorbidities was 21% and the most common comorbidity was hypertension (14).

Although research on FMF related conditions exists, there is a notable lack of studies focusing on comorbidities, particularly among adult FMF patients. Additionally, no studies have explored the relationship between FMF disease severity, treatment strategies, and the presence of comorbidities. Evaluating this situation is particularly important in our country, where FMF is prevalent, and colchicine preparations with different pharmacokinetic properties are used before IL-1 inhibition. As in other CIRDs, awareness of comorbidities in FMF plays an important role in disease management. Since FMF is a disease with a long course, awareness of the accompanying comorbidities will contribute to the patient general well being. This study aimed to address this gap by assessing comorbidities in FMF patients and examining whether severe disease is associated with these comorbidities.

Material and Method

The FMF patients who were followed at Ankara Bilkent City Hospital evaluated retrospectively between May 2019 and March 2024. Patients diagnosed with FMF by a rheumatologist were included in the study. Patients under 18 years of age and patients with any other rheumatological disease accompanying FMF were excluded from the study. Demographic variables, family history of FMF, FMF treatments, and comorbidities of patients were evaluated. The screened comorbidities from records were hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, arrhythmia, chronic kidney disease (CKD), non-renal amyloidosis, chronic obstructive pulmonary disease, asthma, thyroid disease, depression,

demyelinating diseases, neuropathy (non-diabetic), cerebrovascular disease, osteoporosis, and history of malignancy. The accompanying comorbidities were obtained from the medical records of the patients. We grouped patients based on their treatments. Because Türkiye's reimbursement guidelines allow different treatment options according to disease severity in patients with FMF. In Türkiye, coated colchicine is the first-line treatment for FMF, while compressed colchicine (sourced from abroad) is used for patients who are resistant to the coated form. According to the national healthcare reimbursement rules, both forms of colchicine must be attempted before progressing to IL-1 inhibitors. Thus, FMF treatments were categorized into three groups: coated colchicine, compressed colchicine, and IL-1 inhibition. Patients initially receiving coated colchicine were transitioned to compressed colchicine if they exhibited colchicine resistance or intolerance. Colchicine resistance was defined as experiencing at least one attack per month despite taking the maximum tolerated dose of colchicine for a minimum of three months, along with elevated levels of C-reactive protein and serum amyloid A between attacks. If resistance or intolerance continued with compressed colchicine, IL-1 inhibitors were added in for these patients. Additionally, if amyloidosis was detected at any stage, IL-1 inhibition was introduced alongside colchicine treatment.

The study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of Ankara Bilkent City Hospital No 1 approved the study protocol (Date:06/09/2023, Ethical approval number: E1-23-3897). Statistical analyses were conducted using Jamovi v2.3.22 (Sydney, Australia). Both visual methods (such as histograms and probability plots) and analytical methods (like the Kolmogorov-Smirnov test) were employed to assess the normality of the variables. Continuous variables that followed a normal distribution were presented as mean ± standard deviation (SD). Categorical variables were expressed as numbers and percentages. Comparisons between groups were performed using ANOVA for continuous variables and the chi-square test for categorical variables. Further pairwise comparisons were conducted using the Bonferroni method to adjust for multiple testing and minimize the risk of Type I error.

Results

The study included 740 FMF patients. The mean age (SD) of FMF patients was 40.7 (13.3), and 62.4% were female. Among all FMF patients, 75.4% were receiving coated colchicine, 13.3% were receiving IL-1 inhibitors with colchicine, and 11.3% were receiving compressed colchicine. The initial coated colchicine treatment was changed in a total of 24.5% to compressed colchicine, a further step up was done in 13.2% to IL-1 inhibition. 44.7% of all patients had at least one comorbidity. The three most common comorbidities were hypertension (20%), hyperlipidemia (7%) and depression (6.9%).

Table I. Demographic characteristics and comorbidities of the FMF patients

	Coated colchicine, n=588	Compressed colchicine, n=84	IL-1 inhibitor, n=98	All patients	*p value*
Age, year, mean (SD)	41.5 (13.6)	38.1 (12.1)	38.2 (11.9)	40.7 (13.3)	*0.020*
Female, n (%)	355 (60)	54 (64)	53 (54)	462 (60)	*0.350*
Family history of FMF, n (%)	73 (13)	19 (23)	12 (12)	104 (14)	*0.035*
Any comorbidity, n (%)	238 (41)	37 (32)	56 (57)	321 (42)	*0.002*
Hypertension, n (%)	111 (19)	10 (12)	28 (29)	149 (19)	*0.015*
Diabetes mellitus, n (%)	36 (6)	4 (5)	5 (5)	45 (6)	*0.900*
Hyperlipidemia, n (%)	39 (7)	6 (7)	7 (7)	52 (7)	*0.970*
Coronary artery disease, n (%)	11 (2)	2 (2)	1 (1)	14 (2)	*0.800*
Arrhythmia, n (%)	9 (2)	1 (1)	0	10 (1)	*0.640*
Chronic kidney disease, n (%)	13 (2)	0	20 (20)	33 (4)	*<0.001*
Non-renal amyloidosis, n (%)	2 (0.3)	0	1 (1)	3 (0.4)	*0.560*
Chronic obstructive pulmonary disease, n (%)	7 (1)	3 (4)	1 (1)	11 (1)	*0.170*
Asthma, n (%)	33 (6)	3 (4)	3 (3)	39 (5)	*0.580*
Thyroid disease, n (%)	29 (5)	4 (5)	1 (1)	37 (5)	*>0.999*
Depression, n (%)	44 (8)	4 (5)	3 (3)	51 (7)	*0.200*
Demyelinating diseases, n (%)	3 (1)	1 (1)	0	4 (0.5)	*0.430*
Neuropathy (non-diabetes mellitus), n (%)	4 (1)	0	0	4 (0.5)	*>0.999*
Cerebrovascular disease, n (%)	3 (1)	0	3 (3)	6 (1)	*0.060*
Osteoporosis, n (%)	13 (2)	1 (1)	1 (1)	15 (2)	*0.900*
Malignancy, n (%)	3 (0.5)	1 (1)	2 (2)	6 (1)	*0.150*

FMF: Familial Mediterranean fever, IL-1: Interleukin-1, SD: Standard deviation

Demographic characteristics and comorbidities of FMF patients according to treatment groups was shown in Table I. The mean age of patients in the coated colchicine group was higher than in patients receiving both compressed colchicine and IL-1 inhibition. Gender distribution was similar between groups (*p=0.350*). The frequency of patients with a family history of FMF was higher in the compressed colchicine group than in the coated colchicine and IL-1 inhibitor groups (23% vs. 13% and 12%, *p=0.035*, respectively). Comparison of FMF patients comorbidities according to treatment groups; at least one comorbidity was observed in 57% of IL-1 inhibitor group, 41% coated colchicine group, and 32% compressed colchicine group. The frequency of hypertension and chronic kidney disease was higher in the IL-1 inhibitor group than in the coated colchicine and compressed colchicine groups (29% vs. 19% and 12%, *p=0.015*, and 20% vs. 2% and 0%, *p<0.001*, respectively). In the subgroup analysis, any comorbidity was significantly more prevalent in the IL-1 inhibitor group (n=56/98, 57%) compared to the compressed colchicine group (n=27/84, 32%; *p<0.001*) and the coated colchicine group (n=238/588, 41%; *p=0.004*). Hypertension was found to be more common in the IL-1 inhibitor group (29%) compared to the compressed colchicine group (12%; *p=0.006*).

Chronic kidney disease was significantly more common in the IL-1 inhibitor group (n=20/100, 20%) compared to both the compressed colchicine group (0%; *p<0.001*) and the coated colchicine group (n=13/588, 2.2%; *p<0.001*). Family history was more common in the compressed colchicine group (n=19/84, 23%) compared to the coated colchicine group (n=73/588, 12%; *p=0.011*). Other variables, including age, gender, and other comorbidities, showed no statistically significant differences across the treatment groups.

Discussion

The key finding of our study was that almost half of the FMF patients, who were in their 40s on average, had a comorbidity. Our patients with FMF were largely treated with coated colchicine (75.4%), followed by IL-1 inhibitors (13.3%) and compressed colchicine (11.3%), as expected. Treatment adjustments were necessary for 24.5% of patients due to resistance or intolerability. We used treatment groups as a reflection of severe disease. The IL-1 inhibitor group displayed the highest comorbidity burden (57%), particularly with hypertension (29%) and chronic kidney disease (20%), compared to the coated and compressed colchicine groups. This trend suggests that these patients may have more complex clinical profiles, potentially due to organ damage. The findings emphasize the need for individualized screening strategies, particularly for patients with severe disease.

FMF is associated with subclinical or chronic inflammation, which can persist even between acute attacks. Persistent inflammation affects 15-25% of FMF patients, primarily due to active disease or comorbidities like spondyloarthritis and inflammatory bowel disease. Predictors include male gender, M694V homozygosity, colchicine resistance, and musculoskeletal attack dominance. Chronic inflammation is a significant risk factor for developing amyloidosis and other forms of organ damage (10). These findings highlight the importance of monitoring and managing chronic inflammation in FMF patients and carriers to prevent complications and improve outcomes. Colchicine is the primary treatment, but 5-15% of patients may not respond adequately despite optimal dosing (3,15,16). For colchicine-resistant or intolerant patients, IL-1 inhibitors showed substantial efficacy in reducing FMF flare frequency, managing inflammation, and improving patients' quality of life (17). Other treatment options for managing FMF include anti IL-6 agents, intra-articular glucocorticoids, nonsteroidal anti-inflammatory drugs, and disease-modifying anti-rheumatic drugs for chronic arthritis (18). In our study, initial colchicine therapy was adequate for 75% of patients, whereas 25% of patients needed a step up. Among these, 11.3% of the whole cohort could be controlled with compressed colchicine. However, 13.3% required IL-1 inhibitor therapy. We excluded FMF patients who had accompanying other rheumatological diseases.

In fact, all chronic inflammatory rheumatic diseases (CIRDs) are associated with an increased risk of comorbidities, including cardiovascular disease, infections, malignancies, gastrointestinal diseases, osteoporosis, and depression (19,20). These

comorbidities also contribute to higher healthcare costs, lower quality of life, and increased mortality rates in CIRD patients (12). Early detection and management of comorbidities should be an integral part of rheumatology patient care to improve overall health outcomes and reduce the risk of complications (21). When the coincidental comorbidities in FMF patients are analyzed, studies show that the frequency of osteoporosis is higher. In addition, anxiety and depression scores in quality-of-life assessments are more significantly affected (13,22). However, there are a limited number of studies in the literature addressing comorbidities in FMF patients. In a study by Tezcan et al. which evaluated non-FMF-associated comorbidities in 158 adult FMF patients, the comorbidities rate was found to be 21%, with hypertension as the most common one. The comorbidities assessed in this study included hypertension, hypothyroidism, hyperthyroidism, cardiovascular diseases, coronary artery diseases, cerebrovascular diseases, chronic renal disease (non-FMF related), chronic obstructive pulmonary diseases, and diabetes mellitus. In addition, in this study, the authors categorized FMF patients into two groups as mild and severe, based on the international severity scoring system for FMF criteria. Comorbidities were more prevalent in the severe FMF group compared to the mild group (39.1% vs. 18.5%, *p=0.02*) (14). Unlike Tezcan et al, half of all FMF patients in our study had at least one comorbidity. This discrepancy between the two studies may stem from the different FMF-related comorbidities evaluated. Nevertheless, similar to Tezcan et al.'s findings of an increased comorbidity rate among patients with high disease activity, our results also indicated a higher frequency of comorbidities among those receiving IL-1 inhibitor.

In our study, hypertension was the most common comorbidity, affecting 20% of all patients. Its prevalence was notably higher among patients receiving IL-1 inhibitor treatment, where it reached 29%. CKD was observed in 4% of all FMF patients. Additionally, the incidence of CKD alongside hypertension was significantly greater in the IL-1 inhibitor group compared to other groups. The risk of renal disease is known to increase in FMF patients. While amyloidosis related to the disease can affect multiple organs, the risk of renal amyloidosis is particularly elevated, often leading to proteinuria and CKD (23). CKD is thought to be strongly associated with renal amyloidosis. However, as our study relied on medication records rather than file reviews, and because the presence of renal biopsy in CKD patients could not be confirmed, we are unable to present conclusive data regarding amyloidosis. The rate of patients diagnosed with CKD in our study aligns with the reported prevalence of amyloidosis in the literature, which ranges from 2% to 10% (13,24). Chronic inflammation contributes to hypertension pathophysiology, with innate and adaptive immunity raising blood pressure through vascular inflammation and microvascular remodeling (25). The inflammation-hypertension relationship is bidirectional, with each condition potentially worsening the other (26). In patients at risk for renal disease, evaluating and managing coexisting hypertension may improve renal and cardiovascular health. On the other hand, hypertension is known to be one of the risk factors of CKD. High blood pressure increases the risk of development and progression of CKD (27). Hypertension and CKD are more common in patients on IL-1 treatment, likely due to resistant FMF and chronic inflammation. The fact that patients with any comorbidity were more common in the IL-1 inhibitor group may be related to the higher rates of hypertension and CKD in this group. Thus, managing both conditions is crucial for comprehensive FMF care.

Hyperlipidemia is the second most common comorbidity with 7% among all FMF patients. Chronic inflammation is a critical factor in the development of atherosclerosis and cardiovascular diseases, with hyperlipidemia being closely associated with inflammatory status (28). The relationship between inflammation and dyslipidemia is also bidirectional, lipids can activate inflammatory pathways, while cytokines can disrupt lipid metabolism (29). This interaction can create a vicious cycle of inflammation-dyslipidemia-inflammation, perpetuating both conditions (30). In our study, while hyperlipidemia was a notable comorbidity, there was no significant difference in its prevalence across the three patient groups, regardless of the treatment they were receiving. This suggests that other factors, potentially related to the underlying inflammatory process of FMF itself, may contribute more prominently to the

development of hyperlipidemia in these patients.

Depression was the third most common comorbidity among FMF patients in our study, with a prevalence of 6.9%. Inflammatory diseases, including FMF, are linked to higher rates of depression, as chronic inflammation and depression can mutually exacerbate each other (31,32). FMF patients often experience increased rates of depression, frequently accompanied by anxiety and sleep disturbances, which have been associated with higher disease activity (33,34). FMF also restricts daily activities, increases absenteeism and presenteeism, and negatively impacts work performance, which may contribute to mood disorders. Identifying and managing mood and sleep disorders are crucial for improving patient outcomes, as addressing these symptoms can enhance overall quality of life (35). While depression was more prevalent than comorbidities like hyperlipidemia, no significant difference was observed across the three treatment groups. Given the diagnostic challenges of depression, more targeted studies are needed to clarify potential differences between FMF treatment groups.

This study has several limitations. As it was retrospective and based on patient medication records, some data was incomplete. The frequency of comorbidities might differ from that observed in community-based screenings. Another limitation is that acute phase values or disease severity score scales could not be used when comparing treatment groups. While patients with known CKD were included, renal biopsy results were unavailable. Additionally, FMF-related comorbidities and MEFV genetic results could not be assessed due to data access issues, which limited analysis of genetic associations. The switch from coated to compressed colchicine due to intolerance may not indicate true colchicine resistance, meaning transitions in FMF treatment may not always reflect uncontrolled inflammation. Another limitation is the lack of duration data regarding medical treatments and comorbidities.

In conclusion, our retrospective analysis of FMF patients revealed that hypertension, hyperlipidemia, and depression are common comorbidities. While FMF is primarily an inflammatory rheumatologic disease marked by attacks, these comorbidities may be linked to underlying subclinical or chronic inflammation. Particularly in patients requiring IL-1 inhibitors, comprehensive evaluation of comorbidities is essential for better management of end-organ damage, reducing complications, and improving quality of life. It is crucial to assess FMF patients not only for the disease itself but also for accompanying symptoms and comorbidities, employing a multidisciplinary approach when needed.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Effect of Preanesthetic Assessment Timing on Preoperative Anxiety in Ambulatory Surgery Patients

Ambulatuvar Cerrahi Hastalarında Preanestezi Değerlendirme Zamanlamasının Preoperatif Anksiyete Üzerine Etkisi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1448591
Geliş Tarihi | Received: 19.03.2024
Kabul Tarihi | Accepted: 16.10.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Ateş Ayhan N, Hancı V, Özbilgin Ş, Yurtlu BS. Effect of Preanesthetic Assessment Timing on Preoperative Anxiety in Ambulatory Surgery Patients. Hitit Medical Journal 2025;7(1):61-69. https://doi.org/10.52827/hititmedj.1448591

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 21/04/2016 tarihinde Dokuz Eylül Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2016/11-14.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez NAA, BSY Tasarım BSY, ŞÖ Veri Toplama/Veri İşleme: NA, ŞÖ, VH Veri Analizi VH, BSY Makalenin Hazırlanması: NAA, VH, BSY.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Dokuz Eylül University Non-Interventional Research Ethics Committee on 21/04/2016. Decision no: 2016/11-14.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: NAA, BSY Design: BSY, ŞÖ Data Collection/Data Processing: NAA, ŞÖ, VH Data Analysis: VH, BSY Manuscript Preparation: NAA, VH, BSY.
Informed Consent: Written informed consent was obtained from all patients.
Financial Disclosure: There are no financial funds for this article.

Effect of Preanesthetic Assessment Timing on Preoperative Anxiety in Ambulatory Surgery Patients

ABSTRACT

Objective: Preoperative anxiety is a prevalent concern among ambulatory surgery patients. Besides controversial findings between preoperative anesthesia evaluation and anxiety in ambulatory surgical patients, its optimal timing on anxiety levels remains unclear. This study aimed to explore the impact of preoperative anesthesia evaluation timing on anxiety levels in patients undergoing ambulatory surgery.

Material and Method: A prospective, non-randomized, observational study was conducted between May 2016 and August 2016. Adult patients scheduled for elective surgery under local anesthesia with sedation were included. Participants were divided based on the timing of anesthesia evaluation: Group OP (evaluated before surgery) and Group AS (assessed on the day of surgery). Preoperative anxiety was measured using the Spielberger State-Trait Anxiety Inventory (STAI) and Visual Analog Scale (VAS) at two time points: just before preoperative anesthesia evaluation (Score 1) and immediately before surgery (Score 2).

Results: The study comprised 144 patients, with 72 in each group. No significant differences between groups were observed in baseline sociodemographic characteristics ($p>0.05$), except for significantly older patients in Group OP than those in Group AS ($p=0.030$). Median STAI-S, STAI-T, and VAS scores (Score 1) showed no significant differences between groups ($p>0.05$). Both groups significantly increased STAI-S scores between Score 1 and Score 2 measurements ($p=0.015$ for Group OP and $p<0.001$ for Group AS). Nevertheless, changes between Score-1 and Score-2 values of STAI-S scales were similar ($p=0.962$). STAI-S scores were significantly correlated with VAS scores separately in Groups OP and AS at two different time points ($p<0.05$).

Conclusion: The timing of preoperative anesthesia evaluation, whether conducted before or on the day of surgery, did not significantly affect preoperative anxiety levels in ambulatory surgery patients.

Keywords: Ambulatory surgical procedures, anesthetic assessment, preoperative anxiety, state-trait anxiety inventory, visual analogue scale.

ÖZET

Amaç: Preoperatif anksiyete, ambulatuvar cerrahi hastaları arasında yaygın bir endişe kaynağıdır. Ameliyat öncesi anestezi değerlendirmesi ile ambulatuvar cerrahi hastalarındaki anksiyete arasındaki tartışmalı bulgulara rağmen, bu değerlendirmenin anksiyete düzeyleri üzerindeki optimal zamanlaması belirsiz kalmaktadır. Bu çalışmanın amacı, preoperatif anestezi değerlendirmesi zamanının ambulatuvar cerrahi geçirecek hastaların ameliyat öncesi anksiyete düzeyleri üzerindeki etkisini araştırmaktır.

Gereç ve Yöntem: Mayıs 2016 ile Ağustos 2016 arasında, prospektif, non-randomize, gözlemsel bir çalışma planlandı. Lokal anestezi altında sedasyon ile elektif cerrahi planlanan yetişkin hastalar dahil edildi. Katılımcılar, anestezi değerlendirmesinin zamanlamasına göre iki gruba ayrıldı. Anestezi değerlendirmesi cerrahi gününden önce yapılan hastalar Grup OP ve cerrahi günü yapılan hastalar Grup AS olarak tanımlandı. Preoperatif anksiyete, preoperatif anestezi değerlendirmesinden hemen önce (Skor 1) ve cerrahiden hemen önce (Skor 2) olmak üzere iki farklı zaman diliminde Spielberger Durum-Sürekli Anksiyete Envanteri (STAI) ve Görsel Analog Skala (VAS) kullanılarak ölçüldü.

Bulgular: Çalışmada 144 hasta olup, her bir grupta 72 hasta bulunmaktadır. Gruplar arasında temel sosyodemografik özellikler açısından, Grup OP'de anlamlı olarak daha ileri yaşı olan hastalar olması dışında ($p=0,030$), anlamlı bir fark gözlenmedi ($p>0,05$). Medyan STAI-S, STAI-T ve VAS skorları (Skor 1) arasında gruplar arası anlamlı bir fark bulunmadı ($p>0,05$). Her iki grup da Skor 1 ve Skor 2 ölçümleri arasında STAI-S skorlarında anlamlı bir artış gösterdi (Grup OP için $p=0,015$ ve Grup AS için $p<0,001$). Yine de, Skor-1 ve Skor-2 değerleri arasındaki STAI-S ölçeklerindeki değişiklikler benzerdi ($p=0,962$). STAI-S skorları, iki farklı zaman noktasında Grup OP ve AS içinde ayrı ayrı VAS skorları ile anlamlı olarak korele olduğu saptandı ($p<0,05$).

Sonuç: Preoperatif anestezi değerlendirmesinin cerrahi öncesi veya cerrahi gününde gerçekleştirilmiş olmasının, ambulatuvar cerrahi hastalarındaki preoperatif anksiyete düzeyleri üzerinde anlamlı bir etkisi bulunmamaktadır.

Anahtar Sözcükler: Ambulatuvar cerrahi işlemler, anestezi değerlendirme, durum-sürekli anksiyete envanteri, görsel analog skala, preoperatif anksiyete.

Introduction

Preoperative anxiety, stemming from concerns about pain, surgery, unfamiliar surroundings, anticipation of incapacitation, loss of independence, and even mortality, poses a significant challenge (1–3). In the literature, the prevalence of preoperative anxiety in adult patients has been reported as high as 80%, emphasizing the importance of addressing related psychological and physiological aspects (1,4,5). Given the profound effects of preoperative anxiety on information retention, increased anesthetic requirements, and elevated risks of acute and chronic postoperative pain, various strategies, including premedication and informative interventions, have been proposed to manage its multifaceted effects (1,2,6).

Ambulatory surgery has gained popularity over the years in parallel with advances in perioperative anesthetic and surgical techniques (4,7). Preoperative anesthetic assessment has proven helpful in optimizing the preoperative medical status of surgical patients and improving overall care. On the other hand, day-case surgeries, which do not require a prior hospital visit, offer a potential solution to the challenges associated with facility capacity (8,9). However, there are concerns that anxiety and stress levels may be higher in ambulatory surgery patients due to inadequate pre-surgical information (10).

The optimal timing of various pharmacological and nonpharmacological anxiety interventions is unclear (6). A systematic review concluded that the timing of providing pre-surgical information had no significant impact on perioperative anxiety levels (11). In contrast, another study reported that a virtual reality experience immediately before the induction of anesthesia was more effective in reducing preoperative anxiety and distress levels in children compared to providing standard verbal information or performing interventions at outpatient clinics several days before the induction of anesthesia (2). Various studies highlighted the benefits of preoperative anesthesia consultation on anxiety levels (5,12). Additionally, several studies compared the outcomes of preoperative anesthesia given at different times and locations (13,14). However, findings in the literature on the relationship between preoperative anesthetic assessment and anxiety levels are contradictory. Moreover, none of these studies specifically addressed ambulatory surgery patients.

In this context, this study was carried out to determine the preoperative anesthetic assessment's impact on the anxiety levels of ambulatory surgery patients and its optimum timing based on this impact.

Material and Method

Study Design

This study was designed as a prospective, non-randomized, observational study. The Dokuz Eylül University Non-Interventional Research Ethics Committee approved the study protocol on 21.04.2016 (Approval number: 2016/11-14). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Population and Sample

The study population consisted of adult ambulatory patients scheduled for elective plastic and reconstructive surgery under local anesthesia with sedation in Dokuz Eylul University Hospital, Outpatient Surgical Unit, Izmir, Turkey, between May 2016 and August 2016. Patients who were not fluent in Turkish, had III or higher American Society of Anesthesiologists (ASA) physical status, psychiatric or neurological disorders, cooperation problems, impaired cognitive function, and long-standing alcohol use were excluded from the study. The sample was divided into two groups based on the timing of the preoperative anesthesia evaluation: Group OP consisted of the patients who were assessed at the outpatient clinics at least two days before the surgery, and Group AS consisted of the patients who were assessed in the ambulatory surgery unit on the same day of the surgery. The sample size was calculated based on the STAI scores of preoperatively informed patients (15). Accordingly, it was determined that each study group must have at least 63 patients, assuming a power of 95% and an alpha error of 0.05 to detect at least a 15% difference in the STAI scores. Considering a possible drop-out rate of 15%, we included 72 patients in each group. In the end, the study sample consisted of 144 patients. When the target number of 72 patients was reached in each group, the enrollment of new patients in the

study was terminated.

Preoperative Anesthetic Assessment

Per the institutional policy, all patients scheduled for surgery were instructed to visit the Department of Anesthesiology and Reanimation Outpatient Clinics at least two days before the surgery for a preoperative anesthetic assessment. Preoperative anesthetic assessments of patients who have not had a preoperative anesthetic assessment until the day of surgery are conducted by the anesthesia team in the Ambulatory Surgery Unit on the day of surgery.

Table I. Sociodemographic characteristics of the groups

	Group OP (n=72)	Group AS (n=72)	*p*
Age (year) †	40.5 [18.0 – 64.0]	33.0 [18.0 – 80.0]	***0.030****
Age groups ‡			
18-34 Years	28 (38.9)	38 (52.8)	*0.132***
35-50 Years	27 (37.5)	25 (34.7)	
>50 Years	17 (23.6)	9 (12.5)	
Sex ‡			
Female	31 (43.1)	32 (44.4)	*0.999***
Male	41 (56.9)	40 (55.6)	
Educational status ‡			
Primary school	12 (16.7)	15 (20.8)	*0.419***
High school	24 (33.3)	17 (23.6)	
University or higher	36 (50.0)	40 (55.6)	
Occupation ‡			
Worker	25 (34.7)	19 (26.8)	*0.065***
Self-employment	11 (15.3)	22 (31.0)	
Retired	16 (22.2)	12 (16.9)	
Housewife	14 (19.4)	7 (9.9)	
Student	6 (8.3)	11 (15.5)	
Marital status ‡			
Married	47 (65.3)	38 (52.8)	*0.175***
Single	25 (34.7)	34 (47.2)	
Smoking ‡	27 (37.5)	26 (36.1)	*0.999***
Previous anesthesia experience ‡	53 (73.6)	50 (69.4)	*0.712***
Number of operations †	1.0 [1.0 – 6.0]	1.0 [1.0 – 30.0]	*0.741**

Footnote: Table I displays the sociodemographic characteristics of the groups. The † symbol indicates values presented as median and range [Minimum-Maximum]. The ‡ symbol signifies that data are shown in number and percentage format (n (%)). Statistical test symbols are defined as follows: *. The Mann-Whitney U test compares median values between two independent samples. **. The Pearson Chi-Square test is employed to assess the significance of differences in categorical data across groups.

Anesthesia Procedure

A uniform anesthesia protocol featuring local anesthesia under sedation was applied to all patients instead of sedative premedication with anxiolytics. Sedative medications were administered to the patients by the attending anesthesiologists. Dosages were repeated when necessary. Attending surgeons were responsible for administering local anesthesia injections.

Table II. Intra and intergroup comparisons of the groups' STAI-State and Trait Anxiety and VAS scores

		Group OP (n=72)	Group AS (n=72)	*p**
STAI-S †				
	STAI-S-1	33.5 [20.0 – 53.0]	34.0 [20.0 – 57.0]	0.938
	STAI-S-2	38.0 [20.0 – 63.0]	38.5 [20.0 – 63.0]	*0.871*
	*p***	*0.015*	*<0.001*	
	Δ STAI-S †	2.5 [-18.0 – 35.0]	3.0 [-20.0 – 17.0]	*0.962*
STAI-T †				
	STAI-T-1	41.0 [22.0 – 60.0]	37.5 [26.0 – 54.0]	*0.051*
VAS †				
	VAS-1	20.0 [0.0 – 90.0]	25.0 [0.0 – 100.0]	*0.253*
	VAS-2	30.0 [0.0 – 100.0]	30.0 [0.0 – 100.0]	*0.766*
	*p***	***0.010***	*0.510*	
	Δ VAS †	0.0 [-90.0 – 90.0]	0.0 [-40.0 – 50.0]	*0.089*

Footnote: Table II provides intra and intergroup comparisons of the STAI-State and Trait Anxiety and VAS scores. The † symbol indicates that values are presented as median and range [Minimum-Maximum]. The STAI-S and STAI-T represent the State-Trait Anxiety Inventory for State and Trait anxiety, respectively, while VAS stands for Visual Analog Scale. Statistical test symbols are defined as follows: *. The Mann-Whitney U test compares median values between the two independent samples. **. The Wilcoxon test is employed to assess the significance of differences within groups.

Anxiety Level Assessment

The State-Trait Anxiety Inventory (STAI) developed by Spielberger et al. (16) and the Visual Analog Scale (VAS) (1,17) were used to assess patients' anxiety levels. Both tools were administered twice at two-time points: immediately before the preoperative anesthetic assessment (Time Point 1) and immediately before the surgery (Time Point 2).

STAI scale is a 4-point Likert-type scale consisting of two subscales, i.e., STAI-State (STAI-S) and STAI-trait anxiety (STAI-T), each comprising 20 items. While STAI-S reflects acute situational-driven anxiety at a particular moment, STAI-T assesses individual differences in anxiety proneness and a person's general anxiety levels (17, 18). Each item is assigned a score ranging from 1 (not at all) to 4 (very much so). A total score between 20 (no anxiety) and 80 (maximum anxiety) can be obtained from each STAI subscale (10, 12). The Turkish validity studies of the

scale were carried out by Oner and Le Compte (19). STAI-S and STAI-T scores above 44 are considered to indicate high preoperative and general anxiety levels (20).

Table III. Incidences of higher levels of preoperative and general anxiety in the groups.

		Group OP (n=72)	**Group AS** (n=72)	*p*
STAI-State ‡				
	High preoperative anxiety-1 (STAI-S-1, ≥45)	16 (22.2)	10 (13.9)	*0.279*
	High preoperative anxiety-2 (STAI-S-2, ≥45)	23 (31.9)	18 (25.0)	0.460
STAI-Trait ‡	High anxiety-1 (STAI-T-1, ≥45)	24 (33.3)	17 (23.6)	*0.268*

Footnote: Table III summarizes the incidences of higher levels of preoperative and general anxiety in the groups. The ‡ symbol signifies that data are shown in number and percentage format (n (%)). STAI-S and STAI-T represent the State-Trait Anxiety Inventory for State and Trait Anxiety, respectively. The Pearson Chi-Square test is used to assess the significance of differences in categorical data across groups.

In addition, within the scope of VAS, patients were asked to mark their anxiety levels on a scale ranging from 0 (no anxiety) to 100 (worst anxiety imaginable) (1, 17).

Table IV. Correlation analysis of STAI-S, STAI-T, and VAS scores in the study groups.

			Group OP		**Group AS**	
			r	*p*	r	*p*
STAI-S-1	-	**STAI-T-1**	*0.612*	***<0.001***	*0.435*	***<0.001***
STAI-S-1	-	**VAS-1**	*0.522*	***<0.001***	*0.628*	***<0.001***
STAI-T-1	-	**VAS-1**	*0.341*	***0.003***	*0.303*	***0.010***
STAI-S-2	-	**VAS-2**	*0.563*	***<0.001***	*0.747*	***<0.001***

Footnote: This table presents a correlation analysis between STAI-S (State-Trait Anxiety Inventory-State), STAI-T (State-Trait Anxiety Inventory-Trait), and VAS (Visual Analog Scale) scores across two study groups: Group OP and Group AS. The analysis utilizes Spearman's rho correlation coefficients to measure the strength and direction of associations between variables. Correlation coefficients (r) and significance levels (p) are reported for each pair of variables within each group, indicating how anxiety and pain perception measures interrelate in these specific patient cohorts.

Data Collection

Patients' sociodemographic (age, gender, marital, educational, and occupational statuses) and clinical (smoking status, alcohol consumption, previous anesthesia experience) characteristics were collected prospectively via a 10-to-15-minute face-to-face interview conducted by the same researcher. In addition, patients were administered STAI-S, STAI-T, and VAS at Time Points 1 and 2. The anesthesiologists who conducted the preoperative anesthetic assessment were blinded to patients' anxiety levels.

Statistical Analysis

Descriptive statistics obtained from the collected data were expressed as median with minimum and maximum values in the case of continuous variables, such as age and anxiety scores, i.e., STAI-S, STAI-T, and VAS scores, and as numbers and percentage values in the case of categorical variables, such as gender, educational status, and previous anesthesia experience. The normal distribution characteristics of the continuous variables were analyzed using the Shapiro-Wilk test. Non-normally distributed variables between the study groups were compared using the Mann-Whitney U test, i.e., Group OP and Group AS. Categorical variables with more than five expected counts were compared between the study groups using Pearson's chi-square test. Categorical variables with less than five expected counts in RxC tables were compared between the study groups using the Fisher-Freeman-Halton test. The differences in nonparametric anxiety scores assessed at two different time points were compared within the study groups using the Wilcoxon signed-rank test. Correlation analyses between these nonparametric variables were conducted using Spearman's Rho correlation coefficient. Jamovi project 2.3.28 (Jamovi, version 2.3.28.0, 2023, retrieved from https://www.jamovi.org), and JASP 0.17.3 (Jeffreys' Amazing Statistics Program, version 0.17.3, 2023, retrieved from https://jasp-stats.org) software packages were used in the statistical analyses. Probability (p) statistics of < 0.05 were deemed to indicate statistical significance.

Results

One hundred and forty-four patients included in the study sample were divided into Group OP and Group AS, with 72 patients in each group. The median age of the patients in Group OP was significantly higher than in Group AS (40.5 years vs.33.0 years, *p=0.030*). However, a comparison of the groups according to age groups revealed no significant

difference between the groups (*p=0.132*). There was no significant difference between the groups in other baseline sociodemographic characteristics (*p>0.05*) (Table 1).

There was no significant difference between the groups in the STAI-S and STAI-T scores assessed at Time Point 1 (*p=0.938* and *p=0.962*, respectively). On the other hand, the median STAI-S score assessed at Time Point 2 was significantly higher than the median STAI-S score assessed at Time Point 1 in both groups (*p=0.015* for Group OP and *p<0.001* for Group AS). There was no significant difference between the groups in terms of the change in median STAI-S scores assessed at Time Points 1 and 2 (*p=0.962*) (Table 2).

There were no significant differences between the groups in VAS scores assessed at Time Points 1 and 2 (*p>0.05*). In Group OP, the VAS score assessed at Time Point 2 was significantly higher than the VAS score assessed at Time Point 1 (*p=0.010*). There was no significant difference between the VAS scores assessed at different time points in Group AS (*p=0.510*). There was no significant difference between the groups in terms of the change in VAS scores assessed at Time Points 1 and 2 (*p=0.089*) (Table 2).

The rate of patients with high preoperative anxiety levels according to STAI-S scores measured at different time points was higher, albeit not significantly, in Group OP than in Group AS (p>0.05). There was also no significant difference between the groups in the rate of patients with high general anxiety levels (*p=0.268*) (Table 3).

The correlation analysis revealed significant correlations between STAI-S, STAI-T, and VAS scores in Groups OP and AS at different time points (*p<0.05*) (Table 4).

Discussion

The study findings indicated that the timing of preoperative anesthetic assessment—whether conducted before the day of surgery (Group OP) or on the day of surgery (Group AS)—did not significantly impact the preoperative anxiety levels as measured by the STAI-S STAI-T, and VAS scores. The lack of significant differences in STAI-S and STAI-T scores between the groups at the first time point indicated that the initial anxiety levels were similar regardless of the timing of the anesthesia evaluation. In other words, the location and the timing of preoperative anesthetic assessment, whether conducted several days before surgery or on the day of surgery, had no significant impact on preoperative and general anxiety levels in ambulatory surgery patients.

Several studies investigated the relationship between the location and timing of preoperative anesthetic assessment and various aspects of surgical treatment, such as perioperative anxiety levels, cancellation of surgery, and identification of previously unidentified risky medical conditions (2, 5). A limited number of studies have attempted to demonstrate the effect of optimal timing of pre-anesthesia consultation on reducing perioperative anxiety levels in surgical patients (13, 14). In one of these studies, Arellano et al. (14) compared three groups in which the anesthetic assessment was performed at three different times and locations, i.e., in the outpatient clinic a week before surgery, at the bedside upon admission to the hospital, and just outside the operating room immediately before surgery, in terms of perioperative anxiety levels. Consequently, they found that conducting the anesthetic assessment just outside the operating room immediately before surgery significantly reduced patient's anxiety levels. In contrast, Twersky et al. (13) did not find any significant difference in preoperative and postoperative anxiety scores between ambulatory surgical patients whose anesthetic assessments were performed early or on the day of surgery. They found that STAI-T scores did not differ significantly between ambulatory surgical patients whose anesthetic assessments were performed early or on the day of surgery. Similarly, the groups in the current study did not differ in STAI-S scores at either of the two-time points. Our findings also showed that initial anxiety levels, measured both immediately before the preoperative anesthetic assessment and immediately before surgery, were unaffected by the timing of the assessment. Therefore, we believe that the contradictory results regarding the impact of the location and timing of preoperative anesthetic assessments on various aspects of surgical treatment, particularly on patients' anxiety levels, may be due to differences in study designs and patient populations.

Porcar et al. (5) found the rate of patients with high anxiety levels decreased, as evidenced by the decrease in STAI scores after anesthesia consultation. However, although most (72%) of the patients in their sample underwent ambulatory surgery using regional anesthesia, some patients were scheduled for different types of surgery and anesthesia. They stated that giving personal attention to patients and displaying a reassuring attitude helped reduce patients' anxiety levels (5). Akhlaghi et al. (12) demonstrated the positive effect of preoperative anesthetic consultation in reducing preoperative anxiety levels of patients undergoing oral and maxillofacial surgery. Although the STAI was used to assess patients' anxiety levels in these studies (5, 12–14), there were significant differences in terms of the STAI versions used and how the scores were evaluated. To give an example, Porcar et al. (5) used the authors used the short version of the STAI, whereas Akhlaghi et al. (12) used six different severity categories for anxiety based on the total STAI-S and STAI-T scores. In comparison, we separately evaluated the STAI-S and STAI-T scores to assess patients' preoperative and general anxiety levels. In addition, instead of using different severity categories for anxiety, we divided the patients into only two categories based on the definition that an STAI score above 44 indicates high preoperative and general anxiety levels (17,20). This grouping revealed that the proportion of patients with high preoperative anxiety levels, as indicated by STAI-S scores at different time points, was higher in Group OP than in Group AS. However, this difference was not statistically significant. This trend could indicate a potential benefit of same-day assessment in reducing preoperative anxiety, though further research with larger sample sizes might be needed to confirm this observation.

It has been reported in the literature that patients' preoperative anxiety is at its highest level just before being transferred to the operating room (2,13,14). Consistent with this, our study found that both groups showed a significant increase in median STAI-S scores from Time Point 1 to Time Point 2, indicating rising anxiety as surgery approached. However, the magnitude of this change did not differ significantly between the groups, suggesting that while anxiety naturally increases closer to the time of surgery, the timing of the anesthetic assessment did not differentially influence this increase. Contrary to the findings in the literature that a visit by an anesthetist may reduce patients' anxiety levels, we did not find a significant effect of anesthesia consultation on the day of surgery on patients' anxiety levels (14). The short interval between preoperative anesthetic assessment and ambulatory surgical procedures, especially in Group AS, may have prevented the detection of a significant impact.

There are various tools used to assess the anxiety levels of patients, the most commonly used being the STAI. However, the fact that STAI consists of 20 multiple-choice items limits its usability at the bedside (21). The efficacy of VAS as a consistent, simple, and objective tool in assessing anxiety has been demonstrated in the literature (20–23). In parallel, in this study, we used VAS, alongside STAI, to assess the anxiety levels of the patients. Consequently, as in other studies (21), we detected significant correlations between the STAI and VAS scores. The significant correlations observed between STAI-S, STAI-T, and VAS scores across both groups at different time points underscore the robustness of these anxiety measures in reflecting patients' emotional states. Notably, based on VAS scores, we observed a heightened anxiety as surgery approached, but only in Group OP. This suggests that same-day assessment might help mitigate the escalation of anxiety. However, the change in VAS scores between the two time points was not significantly different between the groups, further emphasizing that the assessment timing did not substantially impact anxiety levels. Therefore, we concluded that VAS alone could be a reliable tool for assessing patients' preoperative anxiety levels. Age is considered a potential confounding factor in the assessment of preoperative anxiety among surgical patients (24). Comorbidities and frailty associated with aging may compromise older patients' physiological reserves, potentially increasing their vulnerability to anesthesia and surgery (24,25). While younger adults might also experience preoperative anxiety for different reasons, anesthesia and surgery are significant risk factors for anxiety across age groups. Previous studies on the timing of anesthesia

evaluation have generally reported that age is not a major risk factor for anxiety (3,5,12). However, our study found that patients in Group OP were significantly older than those in Group AS. Although the differences between age groups were not statistically significant, older patients (>50 years) were more commonly found in Group OP, while younger patients (18-34 years) were more prevalent in Group AS. This suggests that as age increases, the risk of preoperative anxiety might also increase. Further large-scale studies are needed to understand better the potential association between age and preoperative anxiety levels.

This study's strengths include assessing patients' anxiety levels at different time points and operating all patients in the same surgical department, which allowed ruling out the confounding effect of varying scheduling practices applied by different outpatient clinics. On the other hand, the fact that the intervals between preoperative anesthetic assessment and surgery were not standardized between the groups is the study's primary limitation. The variability in the time between assessment and surgery could affect anxiety levels differently across patients, potentially introducing variability that could obscure the impact of the timing of the anesthetic assessment. The significantly older age of patients in Group OP compared to Group AS could be a confounding factor influencing preoperative anxiety levels. Prospective studies with more homogeneous demographic characteristics would clarify this issue. Additionally, the study's design as a non-randomized observational study limits the ability to draw causal conclusions. The lack of randomization might introduce selection bias, as patients who chose or were assigned to different timing of assessments could differ in ways not controlled for in the analysis. Lastly, the study was limited to patients undergoing elective plastic and reconstructive surgery under local anesthesia with sedation. This specificity may limit the generalizability of the findings to other types of surgeries or anesthetic approaches.

In conclusion, the study's findings indicated that the location and timing of preoperative anesthetic assessment, whether conducted several days before or on the day of surgery, had no significant impact on preoperative anxiety levels in ambulatory surgery patients. This insight challenges prevailing assumptions in perioperative care practices and underscores the complexity of preoperative anxiety as a multifactorial phenomenon. The consistent increase observed in patients' anxiety levels as the time of surgery approached, regardless of the timing of the preoperative anesthetic assessment, suggests that patients' anxiety may be more deeply rooted in the anticipation of surgery rather than the setting of the preoperative anesthetic assessment.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

The Effect of Serum and Follicle Fluid Melatonin Levels on In-Vitro Fertilization Success Between Polycystic Ovary Syndrome and Unexplained Infertility Patient Groups in In-Vitro Fertilization

Tüp Bebek Tedavisinde Polikistik Over Sendromu ve Açıklanamayan İnfertilite Hasta Gruplarında Serum ve Folikül Sıvısı Melatonin Düzeylerinin Tüp Bebek Başarısı Üzerine Etkisi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1458893
Geliş Tarihi | Received: 26.03.2024
Kabul Tarihi | Accepted: 14.11.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Taşkıran D, Koçak Ö, Ayaz E, Görkem Ü, Toğrul C. The Effect of Serum and Follicle Fluid Melatonin Levels on In-Vitro Fertilization Success Between Polycystic Ovary Syndrome and Unexplained Infertility Patient Groups in In-Vitro Fertilization. Hitit Medical Journal 2025;7(1):70-77. https://doi.org/10.52827/hititmedj.1458893

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 11/08/2021 tarihinde Hitit Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 488.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: DT, ÖK Tasarım: DT, ÖK Veri Toplama/Veri İşleme: DT, ÜG, CT, EA Veri Analizi: DT, ÖK Makalenin Hazırlanması: DT, ÖK.
Hasta Onamı: Tüm hastalardan yazılı bilgilendirilmiş onam ve yayın için izin alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Bilgi: Bu çalışma Deniz Taşkıran'ın uzmanlık tezinden üretilmiştir, 6. Karadeniz Jinekoloji ve Obstetri Kongresi'nde sözlü sunum olarak sunulmuştur (2-4 Haziran 2023).

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Approval for the study was obtained from the Hitit University Clinical Research Ethics Committee on 11/08/2021. Decision no: 488.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: DT, ÖK Design: DT, ÖK Data Collection/Data Processing: DT, ÜG, CT, EA Data Analysis: DT, ÖK Manuscript Preparation: DT, ÖK.
Informed Consent: Written informed consent and consent for publication were obtained from all patients.
Information: This study is derived from Deniz Taşkıran's doctorate thesis, presented as an oral presentation at the 6th Black Sea Gynecology and Obstetrics Congress (June 2-4, 2023).
Financial Disclosure: There are no financial funds for this article.

The Effect of Serum and Follicle Fluid Melatonin Levels on In-Vitro Fertilization Success Between Polycystic Ovary Syndrome and Unexplained Infertility Patient Groups in In-Vitro Fertilization

ABSTRACT

Objective: To investigate the difference in the serum melatonin and follicle fluid melatonin levels at unexplained infertility and polycystic ovary syndrome (PCOS) patients who underwent in-vitro fertilization (IVF) treatment, and to investigate whether the melatonin level affects oocyte quality, embryo number, and clinical pregnancy.

Material and Method: Women with unexplained infertility (n=26) and women with the polycystic ovarian syndrome (n=26) who started IVF treatment were included in this prospective trial. The levels of melatonin in the groups' were tested using the enzyme-linked immunosorbent (ELIZA) method. In addition, the effect of the difference in melatonin levels between the groups on IVF success was investigated.

Results: Patients with the polycystic ovarian syndrome had significantly low serum melatonin levels (*p=0.018*). Melatonin levels in follicular fluid were similar in both groups (*p=0.701*). Total oocyte, M2 oocyte, PN2 oocyte, grade A embryo, second-day embryo count, and the number of transferred embryos did not differ across the groups (*p>0.05)*. There was no significant relationship between serum and follicular fluid melatonin levels (*p>0.05*). There was no significant relationship between clinical pregnancy and melatonin level (*p>0.05*). There was no statistical difference between the groups regarding age, weight, height, and body mass index (*p>0.05*).

Conclusion: In our study, serum melatonin levels were lower in infertile women with polycystic ovary syndrome. This may be due to high melatonin consumption. However, melatonin levels in the serum and follicular fluid had no direct effect on IVF outcomes.

Keywords: Follicular fluid, melatonin, PCOS, unexplained infertility.

ÖZET

Amaç: Açıklanamayan infertilite ve tüp bebek tedavisi gören PKOS (Polikistik Over Sendromu) hastalarında serum ve folikül sıvısı melatonin düzeyleri arasındaki farkı araştırmak ve melatonin düzeyinin oosit kalitesi, embriyo sayısı ve klinik gebelik üzerine etkilerini araştırmak.

Gereç ve Yöntem: Bu prospektif çalışmaya, açıklanamayan infertilitesi olan kadınlar (n=26) ve polikistik over sendromlu (n=26) tüp bebek tedavisine başlayan kadınlar dahil edildi. Grupların serum ve foliküler sıvısındaki melatonin düzeyleri ELIZA yöntemi kullanılarak test edildi. Ayrıca gruplar arasındaki melatonin düzeyi farklılığının IVF başarısına etkisi araştırıldı.

Bulgular: Polikistik over sendromlu hastaların serum melatonin düzeyleri anlamlı düzeyde az idi (*p=0.018*). Foliküler sıvıdaki melatonin düzeyleri her iki grupta da benzerdi (*p=0.701*). Toplam oosit, M2 oosit, PN2 oosit, A sınıfı embriyo, ikinci gün embriyo sayısı ve transfer edilen embriyo sayısı açısından gruplar arasında anlamlı fark yoktu (*p>0.05*). Serum ve foliküler sıvı melatonin düzeyleri arasında anlamlı bir ilişki saptanmadı (*p>0.05*). Klinik gebelik ile melatonin düzeyi arasında anlamlı bir ilişki bulunmadı (p>0.05). Gruplar arasında yaş, kilo, boy ve vücut kitle indeksi açısından istatistiksel fark yoktu (*p>0.05*).

Sonuç: Çalışmamızda polikistik over sendromlu infertil kadınlarda serum melatonin düzeyleri daha düşüktü. Bunun nedeni yüksek melatonin tüketimi olabilir. Ancak serum ve foliküler sıvıdaki melatonin düzeylerinin IVF sonucuna doğrudan bir etkisinin olmadığı görüldü.

Anahtar Sözcükler: Açıklanamayan infertilite, foliküler sıvı, melatonin, PKOS.

Introduction

Traditional definitions of infertility include the failure to conceive with unprotected intercourse for longer than 12 months. This 12-month criteria is accepted as six months for women over 35 years old (1). Approximately 10-30% of infertile couples have no identifiable cause and are termed unexplained infertility (2). Unexplained infertility patients can have a wide range of treatment options, from expectant management to IVF treatment.

Polycystic ovarian syndrome (PCOS) is a complicated endocrinopathy that affects around 10% of women at reproductive age and involves various metabolic processes (3). Free oxygen radicals and anovulation, which develop as a result of oxidative stress in PCOS, are thought to have a negative impact on reproductive function.

The pineal gland produces melatonin (N-acetyl-5-methoxytryptamine), released into the circulatory system. Melatonin has central and peripheral activities and affects the gastrointestinal, cardiovascular, endocrine, and reproductive systems. It has an antigonadotropic effect on the reproductive system. Furthermore, it affects the oocyte's granulosa and luteal cells, suppressing their steroidogenesis (4). Follicular atresia can be observed in PCOS patients due to follicular damage as a result of increased oxidative stress and decreased intrafollicular melatonin levels. Oxidative stress is one of the primary reasons for infertility in women with PCOS, and melatonin is known to have antioxidant properties and inhibitory effects on prooxidant enzymes and proinflammatory cytokines. Melatonin and its metabolites are known to reduce oxidative damage in addition to their direct action. Its anti-inflammatory activity reduces the generation of free radicals and helps to reduce free radical damage. This study aimed to investigate if melatonin affects fertility in subgroups like PCOS and unexplained infertility.

Material and Methods

The study includes 52 infertile women who were admitted to the university hospital's IVF center between September 2021 and March 2022. The Hitit University Faculty of Medicine Clinical Research Ethics Committee authorized this study according to the Declaration of Helsinki (approved number: 488). The study included patients who completed written informed consent forms after receiving extensive verbal and written information. The research was carried out in line with the Helsinki Declaration.

A total of 52 patients were divided into two groups which are PCOS (n=26) as the study group and unexplained infertility (n=26) as the control group. Women who fulfilled the criteria of infertility and had no known cause were accepted as having unexplained infertility. The patients' oligo-anovulation status, polycystic ovarian morphology (PCOM) on transvaginal ultrasonography, and Ferriman-Gallwey scoring as clinical indications of hirsutism were used to diagnose PCOS.

Name, surname, age, weight, height, BMI, menstrual pattern, number of days of menstruation, duration of unprotected intercourse, acne status, and past pregnancies were all noted in patients who participated in the study. The hirsutism of the patients was assessed using the modified Ferriman Gallwey scoring method. The results of a baseline ultrasound, which is performed routinely throughout the evaluation, were recorded. In addition, routinely requested basal hormones (FSH, LH, E2, Prolactin, and AMH) were recorded. Chronic diseases, drug use, smoking, and alcohol use were questioned.

BMI greater than 30 kg/m^2, FSH levels >25 mIU/ml, a male component in infertility, excessive alcohol consumption in the previous six months, smoking at least 20 cigarettes per day, long-term illness, taking melatonin-containing medications or supporting treatments are exclusion criteria.

Patient Blood Serum and Follicular Fluid Collection

Since our study consisted of patients who applied for infertility treatment and were planned for IVF, patients who used the antagonist protocol were included to standardize the number and quality of oocytes and pregnancy status. Oocyte retrieval was conducted at the 35th hour (between 10:00 and 12:00) after hCG treatment when enough follicular development was visible in serial transvaginal ultrasonography. Five ccs of the remnant ovarian follicular fluid was put into a dry tube and stored at -20 °C after the oocytes were separated from the follicular fluid. Approximately 8 cc of patient blood was put into a 10 cc empty dry tube at the same time as the routine blood tests performed

during the patient's hospitalization. In 15 minutes, the blood sample was centrifuged at 4000 rpm for 10 minutes. The obtained supernatants were kept at -20 °C in an Eppendorf test tube (1,5 ml, FIRADMED, polypropylene). The samples were delivered to the laboratory using the cold chain rule once the number of patients had been completed.

Melatonin levels were determined using the Enzyme-linked Immunosorbent Assay Melatonin Kit (catalog number CEA908Ge). After washing with the Human brand, Combi Wash model washing device and reading with the Next Level brand, Alisei model equipment. The sensitivity of the kit is 4.63 pg/mL.

Pregnancy and Oocyte Quality Follow-up

The embryologist noted the number of oocytes, their morphological parameters (MII, PNII, etc.), and the number of embryos after the oocyte pick-up process. On the 14th day after embryo transfer, patients tested for hCG. Patients whose tests were positive for hCG were monitored until fetal heartbeats were detected. The patient was accepted as clinically pregnant when fetal heartbeat was detected. It took about five months to complete the study.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics Client Documentation 26.0 program. Unexplained infertility and PCOS groups were evaluated with Kolmogorov-Smirnov and Shapiro-Wilk normal distribution test, Skewness- Kurtosis tests, and visually normal Q-Q Plot distribution curve, histogram, and box plot. Data that did not fit the normal distribution were analyzed with the Mann-Whitney U Test. The relationship between melatonin level and oocyte number and quality was evaluated with Spearman's correlation test. p<0.05 in the analysis results was considered statistically significant.

Results

In terms of age and BMI, there was no statistically significant difference between unexplained infertility and PCOS infertility groups (*p>0.05* for all). When comparing PCOS to the unexplained group, the cycle duration was significantly longer, and the total number of follicles were significantly higher (*p<0.01*). Table I displays descriptive statistics.

Table I. Descriptive Statistics

	Unexplained Infertile		PCOS Infertile		*p*
	Min-Max (Median)	**Mean±SS**	**Min-Max (Median)**	**Mean±SS**	
Age (year)	21-35 (26.7)	27.1±4.09	23-38 (26.5)	27.92±4.22	*0.762*
BMI (kg/m²)	19-33.3 (24.4)	24.35±3.11	16.9-30 (26.5)	25.72±3.52	*0.084*
Cycle Time	21-45 (28)	27.57±4.5	28-54 (41)	40.08±6.07	***<0.010***
Total Number of Antral Follicles	8-20 (14)	12.15±3.04	10-32 (26)	24.1±4.08	***<0.010***

Independent-Samples, Mann-Whitney U Test, *p<0.05* was considered statistically significant.

When the groups' baseline hormone levels were evaluated, there was no statistically significant difference in FSH, estradiol, or prolactin levels (*p>0.05* for all). LH and AMH levels were considerably higher in PCOS infertile women than in the unexplained group (*p=0.022* and *p=0.01*, respectively). The PCOS infertility group had a statistically low amount of serum melatonin (*p=0.018*). Melatonin levels in follicular fluid were equal in both groups (*p=0.701*). Table II shows the basal hormone and melatonin levels of the groups.

Table II. Basal Hormone and Melatonin Levels of the Groups

	Unexplained Infertile		PCOS Infertile		*p*
	Min-Max (Median)	**Mean±SS**	**Min-Max (Median)**	**Mean±SS**	
FSH (mIU/ml)	1.4-11.4 (6.6)	6.75±2.29	4.3-10.9 (6.65)	6.89±1.74	*0.812*
LH (mIU/ml)	1.02-15.3 (5.4)	5.97±3.17	2.2-19 (7.8)	7.98±3.56	***0.022***
Estradiol (pg/ml)	12-116 (40.45)	46.9±19.7	29.6-70.8 (42.35)	44.22±10.58	*0.777*
Prolactin (ng/ml)	0.5- 42 (15.5)	18.09±10.1	7.5-39 (19.65)	20.31±8.91	*0.282*
AMH (ng/ml)	1.2- 5.7 (2.76)	2.97±1.43	2-13 (4.55)	5.51±2.84	***<0.010***
Serum Melatonin Level (pg/mL)	7.18-50.89 (23.21)	26.13±11.26	5.35-44.29 (17.86)	20.66±9.02	***0.018***
Follicle Fluid Melatonin Level (pg/mL)	6.16-18.3 (12.38)	12.16±3.22	5.94-19.97 (12.81)	12.27±3.63	*0.701*

Independent-Samples, Mann-Whitney U Test, *p<0.05* was considered statistically significant.

There was no statistically significant association between serum melatonin and follicular fluid melatonin levels (*p>0.05*). In terms of total oocyte count, M2

oocyte count, PN2 oocyte count, grade A embryo count, second-day embryo count, and embryo transfer number, there was no significant correlation between serum melatonin level and follicular fluid melatonin level (*p>0.05*, for all). Table III shows the relationship between Melatonin levels, Oocyte Quality, and Embryo Count.

Table III. Correlation of Melatonin Level with Oocyte Quality and Embryo Count

		Correlation Coefficient	*p*
Number of Oocytes Collected	Serum Melatonin Level	-0.143	*0.312*
	Follicular Fluid Melatonin Level	0.155	*0.273*
M2 Oocyte Count	Serum Melatonin Level	-0.147	*0.298*
	Follicular Fluid Melatonin Level	0.153	*0.279*
PN2 Oocyte Count	Serum Melatonin Level	-0.007	*0.958*
	Follicular Fluid Melatonin Level	0.038	*0.791*
Number of Grade A Embryos	Serum Melatonin Level	-0.082	*0.562*
	Follicular Fluid Melatonin Level	0.037	*0.797*
Number of Embryos on Day 2	Serum Melatonin Level	0.050	*0.725*
	Follicular Fluid Melatonin Level	0.049	*0.729*
Number of Patients Who Underwent Embryo Transfer	Serum Melatonin Level	0.049	*0.731*
	Follicular Fluid Melatonin Level	-0.200	0.156

Spearman's correlation test, *p<0.05* was considered statistically significant.

Discussion

In our study, the PCOS group had considerably low serum melatonin levels. According to several studies, oxidative stress caused by reactive oxygen radicals (ROS) is higher in PCOS, and infertility is more common than in the general population (5). While cells need a physiological amount of oxygen to live, free oxygen radicals emerge as a result of these reactions; oxygen superoxide (O_2-), hydrogen peroxide (H_2O_2), and hydroxyl (-OH) reagents must be removed from the environment. During ovulation, reactive oxygen radicals in the follicular environment accelerate oocyte aging (6). Antioxidants like superoxide dismutase (SOD) and glutathione, which eliminate reactive oxygen radicals from the environment, are also in good shape. Melatonin is a powerful antioxidant produced from the pineal gland into the bloodstream and then into the follicular fluid. According to the findings, melatonin treatment reduced oxidative stress by lowering nitric oxide levels and inhibited proinflammatory cytokines (7). It has also been shown that adding melatonin to the culture medium enhances oocyte maturation and lowers the generation of reactive oxygen radicals (8). Various studies have shown that more oxidative stress and melatonin usage are higher in PCOS patients (9-11). Melatonin metabolites, in addition to the direct action of melatonin in lowering oxidative damage, also contribute to reducing oxidative stress through physiological and metabolic effects. Furthermore, because of its anti-inflammatory properties, it aids in reducing free radical production and damage that occurs as a result of the inflammatory response (12). Free oxygen radicals and oxidative stress factors are likely to be higher in the PCOS group, it's reasonable to assume that melatonin consumption will be higher to detoxify them, and that serum melatonin levels will be lower in the PCOS group.

The urinary level of 6-sulphatoxymelatonin, an essential marker for melatonin production, was higher in patients with PCOS than in non-PCOS women (13). Although we did not test 6 sulfateoxymelatonin as a melatonin metabolic marker, endogenous serum melatonin levels were lower in the PCOS group than in the unexplained infertility group. These indicators can be used to determine whether the production is low, or the consumption is high.

Oral melatonin administration in PCOS patients has been shown to reduce oxidative stress, increase oocyte quality, and maybe protect the reproductive system (14). In our study, the serum melatonin level of infertile women with PCOS was lower than the unexplained infertility group, suggesting that it may adversely affect fertility and oocyte quality. However, it was not statistically significant. There was no significant relationship between clinical pregnancy and melatonin levels.

Human studies have found a favorable association between day and night melatonin concentrations and total antioxidant capacity (15). In this regard, increasing endogenous melatonin levels through exogenous melatonin supplementation during

fertilization appears to positively influence the fertilization rate.

The median follicular fluid melatonin level in the PCOS group was 12.81 pg/ml, whereas the follicular fluid melatonin level in the unexplained infertility group was 12.38 pg/ml, and the follicular fluid melatonin level was similar in both groups.
In vitro experiments have shown that women with PCOS have lower levels of melatonin in follicular fluid compared to healthy women (16). Melatonin is hypothesized to minimize oxidative stress, inhibit follicle atresia, and increase follicular maturation in this group of people (17). Unlike in vitro studies, there was no significant difference between the PCOS and unexplained infertility groups in our study.

The total number of oocytes retrieved, the total number of oocytes progressing to MII, the total number of oocytes with PN2, the number of grade A embryos, the number of days two embryos, and the number of embryos that can be transferred were all recorded. One of the most common causes of IVF failure is poor oocyte quality and maturation. Oxidative stress factors in the oocyte may play a role in reduced embryo quality (18). Reactive oxygen radicals and melatonin have directly affected oocyte maturation and fertilization. In a study of 56 patients taking 3 mg/day melatonin supplements and 59 controls, fertilization was found to be higher in the melatonin supplement group (19). The melatonin levels in follicular fluid and serum did not affect the quality and maturation of oocytes in our study. Although exogenous melatonin has been demonstrated to have a favorable effect on oocyte maturation, endogenous follicular fluid and serum melatonin levels did not correlate with the number of oocytes or the number of good-quality oocytes in our study (14). There was no significant relationship between clinical pregnancy and melatonin levels. The effect of melatonin on infertility is not fully understood (20).

Because melatonin is produced in various tissues and organs, the mean serum melatonin level is likely to be higher than the mean follicular fluid. Recent studies show that melatonin is synthesized in small amounts in a wide variety of tissues and has paracrine and autocrine effects (21). In our study, the mean serum melatonin level was 23.39±10.12 pg/ml, and the mean follicular fluid melatonin fluid level was 12.21±3.42 pg/ml. In another study, the follicular fluid melatonin level was found to be 20.9 ± 3.6 pg/ml in the PCOS group, and it was higher than we found (22). Brzezinski et al. discovered that the level of melatonin in the follicular fluid before ovulation was higher than the level of melatonin in the plasma (22,23).

In contrast to this study, serum melatonin levels were higher than follicular fluid melatonin levels. This may be because Brzezinski et al. utilized the RIA method while we used the ELISA. Because melatonin is produced by various tissues and melatonin consumption may be higher during ovulation due to increased oxidative stress, the follicular fluid level of melatonin is expected to be lower than the serum level. The PCOS group had a median AMH level of 4.55 ng/ml, while the unexplained infertile group had a median AMH level of 2.76 ng/ml. The PCOS group's AMH level was statistically greater. Due to the lack of an international standard, AMH currently plays no significant role in the diagnosis and treatment of PCOS. Many studies have shown that AMH levels are higher in PCOS patients (24,25). The total number of oocytes collected in both groups was compared, the PCOS group had a total oocyte count of 9.5.

In contrast, the unexplained infertility group had a median total oocyte count of 4. It was statistically higher in the PCOS group ($p<0.01$). The level of AMH can help us forecast ovarian reserve and oocyte count.

The median LH level measured on the second day of the menstrual cycle in women in the PCOS group was 7.83 mIU/ml, and 5.41 mIU/ml in the unexplained infertile group. It was statistically higher in PCOS. In the past, a higher LH level than FSH level was used as an indicator for PCOS. In some studies, it has been shown that the LH level is high in PCOS (26). However, an elevated LH level is not a diagnostic criteria for PCOS. Androgen increase and phenotypic changes due to LH elevation may be symptoms of PCOS.

When the two groups were compared, the median FSH value was 6.65 mIU/ml in the PCOS group and 6.60 mIU/ml in the unexplained infertility group, and it was similar in both groups. FSH level above

10 mIU/mL is considered a poor ovarian response, indicating a decreased ovarian reserve (27). In addition, estradiol levels were also found to be similar in both groups. Therefore, it shows that the groups are similar in ovarian response.

When the menstruation cycles of the two groups were compared, women with PCOS had a longer period. This is because women with PCOS are more likely to have oligo-ovulation. Women with oligomenorrhea whom have fewer than nine menstrual cycles per year is frequently seen in PCOS patients (28). The cycle in the PCOS group was 40.08±6.07 days in our study. Compared to the unexplained infertility group, these women's cycles lasted much longer.

There was no difference between the two groups in terms of age, height, weight, and BMI. However, the unexplained infertility group had a median age of 26.7 years, while the PCOS group had 26.5 years. The unexplained infertility group had a median BMI of 24.4 kg/m^2, while the PCOS group had a median BMI of 26.5 kg/m^2, with no statistical difference. More than half of women with PCOS are obese (29). Therefore, to exclude obesity-related factors in the PCOS group, patients having a BMI of more than 30 kg/m^2 were excluded from the study.

The limitations of this study, the patients' levels of endogenous melatonin were measured and compared to the follicular fluid. Therefore, melatonin's production and elimination processes were not studied. These processes were not included because the study's principal objective was to correlate follicular fluid and serum melatonin and its effect on IVF. To investigate these phases, more comprehensive in-vitro experiments can be planned.

Conclusion

The levels of melatonin in follicular fluid were similar in the PCOS and unexplained infertility groups. The antioxidant impact of melatonin in the follicular fluid is identical to the unexplained infertility group, despite the high oxidative stress reported in PCOS. This shows that oxidative stress markers in PCOS follicular fluid may be lower than previously thought. Additionally, melatonin levels did not affect oocyte and embryo quality. Although exogenous melatonin treatment has been shown to improve the rate of pregnancy in numerous studies, we discovered that endogenous melatonin levels did not affect the pregnancy rate. In our study, the serum melatonin level was lower in the PCOS group than in the unexplained infertility group. However, melatonin levels were high in PCOS patients in various studies. Therefore, it is expected that serum melatonin levels may be low in PCOS due to the consumption of melatonin, which is an antioxidant.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Evaluation of Ultrasound Imaging in Developmental Hip Dysplasia with Artificial Intelligence

Gelişimsel Kalça Displazisinde Ultrason Görüntülemenin Yapay Zeka ile Değerlendirilmesi

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1472551
Geliş Tarihi | Received: 23.04.2024
Kabul Tarihi | Accepted: 16.10.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Olçar HA, Köksal AS, Altıntaş O, et. al. Evaluation of Ultrasound Imaging in Developmental Hip Dysplasia with Artificial Intelligence. Hitit Medical Journal 2025;7(1):78-87. https://doi.org/10.52827/hititmedj.1472551

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma, Yozgat Bozok Üniversitesi Tıp Fakültesi Etik Kurulu tarafından 10.02.2022 tarihinde onaylandı (EK No: 2017-KAEK-189_2022.02.10_03).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: HAO Tasarım: MK, GY Veri Toplama/Veri İşleme: GY, GG, ASK Veri Analizi: ASK, OA, BT, SBY, BÇ Makalenin Hazırlanması: HAO, ASK
Hasta Onamı: Katılımcıların ebeveynlerinden yazılı onam alındı.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Bilgi: Yozgat Bozok Üniversitesinin 16-17-18 Mayıs 2024 tarihlerinde gerçekleştireceği "Endüstri 5.0, Yapay Zekâ ve Dijitalleşme" temalı sempozyuma bildiri olarak gönderilmiştir.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: The study was approved by the Yozgat Bozok University Faculty of Medicine Ethics Committee on 10.02.2022 (IRB No. 2017-KAEK-189_2022.02.10_03)
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: HAO Design: MK, GY Data Collection/Data Processing: GY, GG, ASK Data Analysis: ASK, OA, BT, SBY, BÇ Manuscript Preparation: HAO, ASK
Informed Consent: Our University Clinical Research Ethics Committee has confirmed that no consent for publication from patients is required.
Financial Disclosure: There are no financial funds for this article.
Information: It was sent as a paper to the symposium themed "Industry 5.0, Artificial Intelligence and Digitalization" to be held by Yozgat Bozok University on 16-17-18 May 2024.

Evaluation of Ultrasound Imaging in Developmental Hip Dysplasia with Artificial Intelligence

ABSTRACT

Objective: Developmental hip dysplasia is a common condition that starts in infancy. With the introduction of machine learning (artificial intelligence, AI) into medicine, the early diagnosis of disease and the success of treatment have increased significantly. This study aims to determine the accuracy of ultrasound images from ultrasound videos used in the developmental hip dysplasia screening program using machine learning techniques.

Material and Method: The study involved the extraction of ultrasound image features using the Local Binary Pattern (LBP) method. The ultrasound image dataset was then prepared to evaluate the effectiveness of various machine learning approaches, including Decision Tree (DT), Random Forest (RF), K-Nearest Neighbour (KNN), Gradient Boosting (GB), Support Vector Machines (SVM), Naïve Bayes (NB), Logistic Regression (LR), and Multilayer Perceptron (MLP).

Results: RF algorithm performed very well, recording the highest correct image rate. The study was generally considered successful and it is believed that the resulting model will be useful in the early diagnosis of developmental hip dysplasia.

Conclusion: RF algorithm recorded the highest correct image rate, performing very well at 87.62% compared to other tested algorithms. The study was generally considered successful and the resulting model is believed to be useful in the early diagnosis of developmental hip dysplasia.

Keywords: Algorithms, classification, deep learning, developmental dysplasia of the hip, machine learning, artificial intelligence, ultrasonography.

ÖZET

Amaç: Gelişimsel kalça displazisi, bebeklik döneminde ortaya çıkan yaygın bir hastalıktır. Makine öğreniminin (yapay zeka, AI) tıp alanına girmesi ile hastalıkların erken tanısını ve tedavi başarısını önemli oranda artırmaktadır. Bu çalışma, makine öğrenme tekniklerini (yapay zeka) kullanarak gelişimsel kalça displazisi tarama programında kullanılan ultrason videolarından ultrason görüntüsünün doğruluğunun belirlenmesi amaçlamaktadır.

Gereç ve Yöntem: Çalışma, Lokal İkili Model (LBP) metodolojisi aracılığıyla ultrason görüntü özelliklerinin çıkarılmasını içeriyordu. Daha sonra, 'Decision Tree (DT), Random Forest (RF), K-Nearest Neighbour (KNN), Gradient Boosting (GB), Support Vector Machines (SVM), Naïve Bayes (NB), Linear Regression (LR), and Multilayer Perceptron (MLP)' dahil olmak üzere farklı makine öğrenimi yaklaşımlarının etkinliğini değerlendirmek için ultrason görüntü veri kümesini hazırlandı.

Bulgular: RF algoritması, test edilen diğer algoritmalarla karşılaştırıldığında %87,62 ile çok iyi performans göstererek en yüksek doğru görüntü oranını kaydetti. Çalışma genel olarak başarılı kabul edildi ve ortaya çıkan modelin gelişimsel kalça displazisinin erken teşhisinde faydalı olacağına inanılıyor.

Sonuç: RF algoritması en yüksek doğru görüntü oranını kaydederek çok iyi bir performans sergilemektedir. Çalışma genel olarak başarılı sayıldı ve elde edilen modelin gelişimsel kalça displazisi' nin erken teşhisinde yardımcı olacağı düşünülmektedir.

Anahtar Sözcükler: Algoritma, derin öğrenme, gelişimsel kalça displazisi, makine öğrenmesi, yapay zeka, sınıflandırma, ultrasonografi.

Introduction

Developmental dysplasia of the hip (DDH) is a frequently-occurring ailment among infants, caused by genetic, intrauterine and cultural factors. It has an incidence rate ranging between 2% and 5% (1). The condition can be grouped into various types, including acetabular dysplasia, instability, subluxation and complete dislocation (2). Failure to promptly receive a diagnosis and treatment may result in more intricate procedures, including hip replacement, in the future (3).

Current clinical practice for DDH entails clinical examination, assessment of risk factors, and radiological imaging (4,5). Radiography is widely regarded as an effective diagnostic tool for DDH, notwithstanding its potential drawbacks in terms of radiation exposure and limited information for neonatal hips due to incomplete ossification of cartilage. Ultrasonography is an efficient method for screening DDH in the first six months of an infant's life because it facilitates comprehensive static and dynamic imaging of the hip joint. However, ultrasound imaging of the hip joint poses technical challenges. The ultrasound technique for assessing the condition of infants' hips was introduced by Graf in the 1980s (6). Currently, Graf's approach is the most widely used technique for diagnosing DDH using coronal plane ultrasound images. However, there are numerous ongoing debates about the effectiveness of ultrasound in enabling early and precise diagnosis and guidance for treatment (4,5). In keeping with Graf's methodology, measurement and classification are executed based on the standard plane, encompassing the iliac crest, the base of the acetabulum, and the acetabular labrum. However, establishing the precise plane that demarcates the image slice of a neonatal hip is often difficult, and drawing three lines heavily depends on the physician's precise application (7,8).

The extensive utilization of machine learning and deep learning techniques has been observed for the diagnosis of various diseases (9). Among deep learning architectures that have been described in existing literature, Convolutional Neural Networks (CNNs) are frequently applied (10). Automatic classification of hip dysplasia is a recent and developing field, involving data collection, data preprocessing, feature extraction, training, and testing on images (11).

In recent years, researchers have demonstrated that a close connection between engineering labs and real-world practice is necessary to achieve meaningful results in ultrasound research (12). Hip ultrasonography is the established diagnostic tool for DDH necessitating precise assessment with standard plane images to guarantee proper diagnosis. Nonetheless, it has been reported that imaging may be undependable, and, thus, accurate imaging tests are indispensable for precise diagnosis. Incorrect body positioning or poor image quality may compromise the quality of images, significantly affecting diagnosis impacts. In recent years, scholars have conducted research on the efficacy of deep learning methods to offer automated assurance of precise diagnosis by operators (11,13,14). This can prove to be a useful aid for inexperienced operators.

The evaluation of the ultrasound image used in the developmental hip dysplasia screening programme consists of three steps. The first step is to correctly locate the reference points on the ultrasound, the second step is to draw lines from the correctly located reference points and make angle measurements according to these lines, and the third step is to stage the hip according to the degree of measurement as a normal hip or a DHH hip. There are studies on the second and third steps (11, 14). There are not enough studies in the literature on the first step, where physician experience is important.

The study's significance lies in the scarcity of research into the precision of images used in diagnosing DDH and the approaches taken. It offers evidence that machine learning techniques can automatically identify appropriate images. A novel dataset and unexplored methodology are employed in the study, which fills a gap in the research and results in acceptable precision and swift functionality. This highlights the unique value of our study. The aim of our study is to use artificial intelligence to distinguish between the presence (correct image) or absence (incorrect image) of reference points used in the diagnosis of DDH in ultrasound images taken during DDH scans. Thus, artificial intelligence that can perform ultrasound evaluation can pave the way for young physicians to meet their need for experience.

Material and Method

Ethical Approval

The study was approved by the Yozgat Bozok University Faculty of Medicine Ethics Committee on 10.02.2022 (IRB No. 2017-KAEK-189_2022.02.10_03) in accordance with the Declaration of Helsinki, and written informed consent was obtained from the parents of the participants.

Study Design and Data Collection

In this study, ultrasound records "ACUSON S2000 Ultrasound System, HELX Evolution with Touch Control (Siemens Healthineers, Germany") of both the right and left hips of 100 infants collected from Yozgat City Hospital were examined. The Local Binary Patterns (LBP) texture analysis method was utilised for gathering features from these images, and subsequently building a dataset. In the study, 80% of the dataset was used as training dataset to train machine learning algorithms to classify images according to their correctness. The remaining 20% of the dataset were reserved for testing purposes. A range of machine learning algorithms, such as Support Vector Machines (SVM), Naive Bayes (NB), Logistic Regression (LR), Random Forest (RF), K-Nearest Neighbours (KNN), Decision Tree (DT), Gradient Boosting (GB), and Multilayer Perceptron (MLP), were employed to perform this classification. Inclusion criteria: Infants aged 40-45 days, standard cross-sectional coronal plane ultrasound scans performed in the lateral decubitus position, using a 7.5 MHz linear ultrasound probe, acquisition of images representing normal or dysplastic hips, with measurement reference points specified in the hip scan programme.

Exclusion criteria: Infants with a history of previous hip surgery or unrelated congenital anomalies, presence of neuromuscular diseases or syndromes that may contribute to congenital hip dislocation, images taken in positions other than lateral decubitus, hip ultrasound measurements outside the specified age range of 40-45 days, situations where the infant's distress prevents imaging, ultrasound scans performed for indications other than DDH.

The study utilized Python® programming language, along with the Scikit-Learn® and OpenCV® libraries. The experimental setup included a computer with a 12th generation Intel® Core™ i7 processor, 32 GB RAM, and a 1 TB M.2 SSD.

Dataset and Data Augmentation

In the study, 200 video recordings were created from both the right and left hips of one hundred newborns. Then, eighteen images were captured from each video recording at equal intervals (three images per second). Thus, a dataset consisting of three thousand six hundred images was obtained. Neonatal hip ultrasound was performed with the infant in the lateral decubitus position, with the hip and knee in semi-flexion and 15-20 degrees of internal rotation (6). In this position, the greater trochanter of the femur was imaged exactly laterally, under the probe, in the anteroposterior plane. The anatomical structures of the tissues of a healthy developed hip are shown schematically (Figure I). A standard section was used in the coronal plane so that the ultrasound scans could be compared and everyone could take measurements in the same plane (6). There are three important reference points that should be present in the standard section: The ilium should be parallel to the skin, the labrum should be visible, and the ossified end of the ilium should be visible in the acetabulum (6).

Hip ultrasound images were obtained from healthy or dysplastic newborns aged 40-45 days in the newborn hip screening programme. Ultrasound images from the screening programme were graded by an experienced radiologist and a paediatric orthopaedic specialist on the basis of whether the 3 reference points, for which physician experience is important, were correctly included in the image area. Failure to detect the three reference points used to diagnose and classify DDH (acetabular labrum, acetabular edge and inferior iliac edge) was used as a faulty image, and the ability to detect this was used as a correct image in the artificial intelligence training.

The images were evaluated by a radiologist and an experienced paediatric orthopaedic physician. The radiologist categorized the images as either correct or incorrect (Figure I), identifying 1522 as correct and 2078 as incorrect. These experts also evaluated these images and determined that 8 hips were Type 2 and 192 hips were Type 1. This shows that the dataset contains data from both healthy and unhealthy individuals.

Feature extraction is a widely used procedure in machine learning that involves picking a subset of data-specific features to apply a learning algorithm. The ultimate goal is to determine the most minimal number of features for a given problem domain that precisely represent it (15). One well-known method for accomplishing this is LBP.

The LBP works with greater efficiency and reliability on grayscale images due to its capacity to process only one operation per pixel. Besides being user-friendly, it offers improved speed advantages for handling larger datasets and real-time applications (16). This quality of LBP was the primary reason for utilizing it in this study.

The LBP method of extracting features was employed on each classified image, resulting in 10 column features being extracted. An extra column containing the class feature (correct or incorrect) was also included, resulting in a 1x11 array for each image. The features of every image were then added as lines in a CSV file, resulting in the creation of a dataset measuring 3600x11. Data augmentation is a technique that can enhance the effectiveness of machine learning and deep learning algorithms and regularize the datasets used by (17).

Initially, it was believed that any lack of balance between the classes within the dataset could negatively impact the success rate. To address this concern, different data augmentation methods were employed, including vertical and horizontal shift, as well as cropping and scaling techniques. As a consequence, the quantity of data assigned to the correct class rose to 2078, thus rectifying the imbalance between the classes. This resulted in a dataset consisting of 4156 data points, which were utilised to develop and test the model as per the machine learning methodologies detailed in section 2. The success rates achieved are presented in the Results section.

After rectifying the unevenness between the classes in the dataset, data expansion techniques were implemented once more to amplify the dataset. Nevertheless, as no enhancement on the achievement rate was witnessed, the study continued with a dataset comprising 4156 data points.

Machine Learning Algorithms

The research employed the widely accepted K-Nearest Neighbours machine learning algorithm that is commonly utilised in regression and classification tasks. This algorithm allows a point to be classified based on the closest previously classified K number of points. Its primary aim is to use majority voting for the label prediction of a test data point (18).

Decision trees represent a classification algorithm that iteratively segments the dataset. This tree features a root node, internal nodes as well as terminal nodes (leaves), while the nodes of the tree consist of characteristics from the dataset, and the leaves are composed of predetermined values located in the outcome column. Each new example in the dataset is allocated to an appropriate class within the tree based on the pre-existing attribute values. To perform this placement, the relevant instance is moved within the tree and its classification is determined (19).

Gradient Boosting is a machine learning algorithm used for classification. The process involves training models in succession, with each subsequent model aiming to reduce errors from the previous one. The following steps are taken: Firstly, a model is created for predicting from the training dataset. Residuals are then calculated based on the difference between observed and predicted values. A new model is subsequently generated from the residuals to produce fresh predictions. Following this, the sequence is repeated until the residuals are reduced to a minimum or a specific threshold value is attained (19).

The Random Forest algorithm is a machine learning technique that was developed in 2001 by Leo Breiman (20). It can be used for both regression and classification problems, and its structure is composed of numerous decision trees. By processing data using multiple decision trees, the algorithm is able to provide precise predictions by averaging the acquired predictions. This approach also helps to prevent overfitting, which is a common issue in the decision tree method.

Naive Bayes is a statistical algorithm for classification based on probabilities. It is trained for supervised learning and applicable in practical real-world scenarios. The approach is simple as it uses Bayes' theorem to calculate probabilities, making it easy to understand and useful in limiting complexity. The algorithm determines the probability of an instance

belonging to a target category, making it a valuable tool in various applications (21).

Table I. Evaluation metrics for machine learning methods employed

Model	RF	GB	KNN	DT	MLP	LR	NB	SVM
Accuracy	0.8762	0.8582	0.8474	0.8125	0.7536	0.6478	0.6214	0.5853
Sensitivity	0.8945	0.8784	0.8601	0.8326	0.7638	0.7041	0.7706	0.7569
Specificity	0.8561	0.8359	0.8333	0.7904	0.7424	0.5859	0.4571	0.3965
PPV	0.8725	0.8549	0.8503	0.8139	0.7655	0.6518	0.6098	0.5800
F1 Score	0.8834	0.8665	0.8552	0.8231	0.7646	0.6770	0.6809	0.6567
Youden J Index	0.7506	0.7143	0.6934	0.6230	0.5062	0.2900	0.2277	0.1533

RF: Random Forest, GB: Gradient Boosting, KNN: K-Nearest Neighbours, DT: Decision Tree, MLP: Multilayer Perceptron, LR: Logistic Regression, NB: Naive Bayes, SVM: Support Vector Machine, PPV: Positive Predictive Value.

The Support Vector Machine constitutes another algorithm often employed in the realm of machine learning. SVM aims to distinguish between classes by measuring distances among instances belonging to respective categories. Significantly, to achieve high classification success, the hyperplane must remain distant from data points of other classes, a feat accomplished through the formation of hyperplanes. Furthermore, support vectors are determined by calculating the points closest to the classifier's margin (22).

Table II. Resource usage of machine learning techniques

Model	RF	NB	MLP	LR	KNN	DT	GB	SVM
Training time (sec)	0.8604	0.003	3.7491	0.0312	0	0.0227	3.6078	0.1884
Memory usage in training (MB)	3.4922	0.0117	1.6094	0.25	0.0977	0	1.4844	0.5977
CPU usage in training (%)	41.8	0	0	0	0	0	61.5	83.6
Test time (sec)	0	0	0	0	0.0156	0	0	0.0313
Memory usage in test (MB)	0.0078	0	0.2734	0	0.0547	0	0.0117	0.1445
CPU usage in test (%)	0	0	0	0	0	0	0	48.8

(RF: Random Forest, GB: Gradient Boosting, KNN: K-Nearest Neighbours, DT: Decision Tree, MLP: Multilayer Perceptron, LR: Logistic Regression, NB: Naive Bayes, SVM: Support Vector Machine).

Logistic regression is a widely utilized model in machine learning, particularly effective in binary classification problems. This model analyses relationships within a dataset, modelling the connection between input variables and the probability of an event, making it a machine learning model that generates predictions (23).

Table III. Resource usage of machine learning techniques

Model	RF	NB	MLP	LR	KNN	DT	GB	SVM
Training time (sec)	0.8604	0.003	3.7491	0.0312	0	0.0227	3.6078	0.1884
Memory usage in training (MB)	3.4922	0.0117	1.6094	0.25	0.0977	0	1.4844	0.5977
CPU usage in training (%)	41.8	0	0	0	0	0	61.5	83.6
Test time (sec)	0	0	0	0	0.0156	0	0	0.0313
Memory usage in test (MB)	0.0078	0	0.2734	0	0.0547	0	0.0117	0.1445
CPU usage in test (%)	0	0	0	0	0	0	0	48.8

RF: Random Forest, GB: Gradient Boosting, KNN: K-Nearest Neighbours, DT: Decision Tree, MLP: Multilayer Perceptron, LR: Logistic Regression, NB: Naive Bayes, SVM: Support Vector Machine

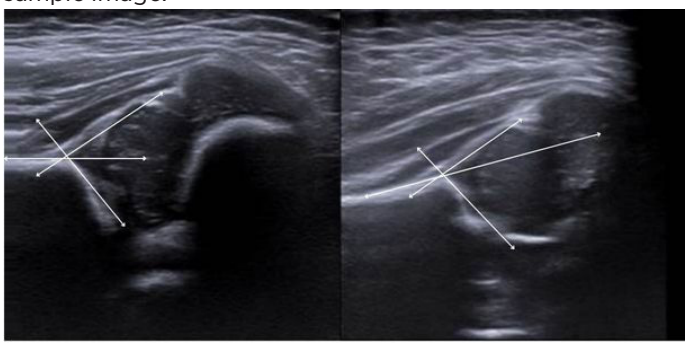
Multilayer perceptions are often used for tasks such as recognizing patterns, interpolating, and classifying data. They are an improved type of the Perception neural network, which was developed in the early 1960s and has several limitations (24).

Statistical Analysis

The learning performance of different algorithms was evaluated using the traditional Receiver Operating Characteristic (ROC) curve and Area Under the Curve (AUC). Accuracy, sensitivity, specificity, positive predictive value, F1 score, and Youden J Index were calculated for each algorithm (Figure II). The F1 Score is used in statistical analysis to assess the balance between precision and recall in classification tasks, providing a single value that combines both measures and is particularly useful for evaluating the overall performance of machine learning models (25). The Youden J Index, employed in statistical analysis, quantifies the overall accuracy of a diagnostic or classification test by optimizing the trade-off between sensitivity and specificity, offering a single metric that encapsulates the model's ability to correctly identify both positive and negative instances (26). "IBM SPSS Statistics for Windows, Version 27.0" program was used for the ROC (receiver operating characteristic) curve and AUC (Area under the ROC Curve). The main criterion for evaluating the effectiveness of a classification

algorithm is the accuracy rate (27).

Figure I. Correct and Incorrect Images from the dataset, the iliac bone should be parallel to the skin, the Labrum should be visible, and the ossified end of the ilium should be seen in the acetabulum (6). Change in the drawing due to the iliac bone not being parallel to the skin, left is correct, right is incorrect. sample image.



Results

The average age of the babies in the study was 40-45 days. 47% of the participants were girls and 53% were boys. The distribution of hips studied was 50% left hip and 50% right hip. Of the infants, 60 were the first babies in the family and 40 were the next babies in the family. There were 45 caesarean sections and 55 normal births.

Figure II. The calculation formulas (TP: True Positive, TN: True Negative, FP: False Positive, FN: False Negative, PPV: Positive Predictive Value).

$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{FP} + \text{TN} + \text{FN}}$$

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

$$\text{F1 Score} = 2 * \frac{\text{Sensitivity} * \text{PPV}}{\text{Sensitivity} + \text{PPV}}$$

$$\text{J Statistic Youden Index} = \text{Sensitivity} + \text{Specificity} - 1$$

Table I of the study displays the accuracy, sensitivity, specificity, positive predictive value, F1 score, and Youden J Index of the applied machine learning techniques. Examination of the results suggests that the most effective approach was the RF method, as evidenced by sensitivity, specificity, positive predictive value, F1 score, and Youden J Index of 0.8762, 0.8945, 0.8561, 0.8725, 0.8834, and 0.7506, respectively. The ROC curves of different machine learning techniques are shown in Figure III.

Figure III. ROC Curves of Machine Learning Techniques (RF: Random Forest, GB: Gradient Boosting, KNN: K-Nearest Neighbours, DT: Decision Tree, NB: Naive Bayes, MLP: Multilayer Perceptron, SVM: Support Vector Machine, LR: Logistic Regression)

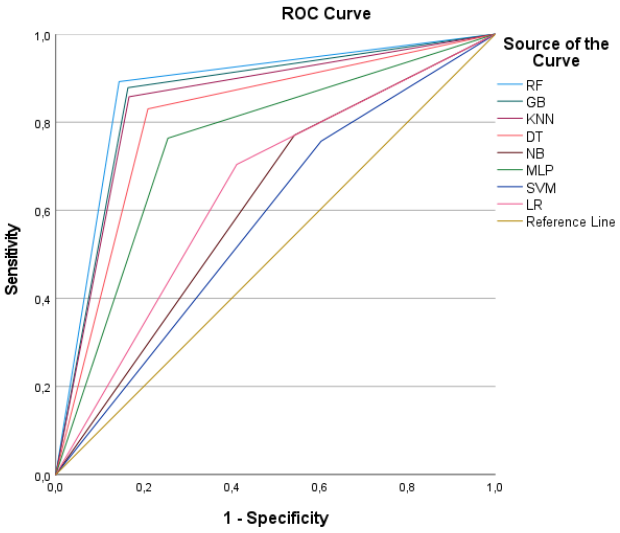


Table II presents a comparison of the training and test times, training and test memory usage, and training and test processor usage across the algorithms utilized in the study. Some of the algorithms recorded a resource usage of zero due to their minimal resource consumption. Notably, the RF algorithm demonstrated impressive performance while utilizing the least resources in test time (0), test memory usage (0.0078), and test processor usage (0). The test time and processor usage are displayed as zero because they are very close to zero. The system under study displays them as zero.

Discussion

Acquiring the appropriate image is crucial for automating an accurate diagnosis of DDH. This research employed machine learning algorithms to obtain accurate images from ultrasound recordings. A specially prepared dataset measuring 4156x11 was utilised in this study. Eight varied machine learning algorithms were tested, and the Random Forest algorithm presented the highest rate of achievement and productivity.

AI's image detection capabilities have been reported in various fields, including the detection of lung CT nodules, automatic detection of COVID-19 using chest X-ray images, and the identification of brain tumors and Alzheimer's lesions through brain MRI scans (13). CNNs are purportedly benefit from diagnosing DDH by examining anteroposterior pelvic radiographs (28). Zhang and colleagues (28) have reported that a deep learning system was trained and optimized using 9081 radiographs. Subsequently, 1138 test radiographs were employed to compare diagnoses made by both the deep learning system and clinicians. The deep learning system's diagnostic accuracy for identifying hip dislocations was determined by the area under the receiver operating characteristic curve (AUC), sensitivity and specificity, scoring 0.975, 276/289 (95.5%) and 1978/1987 (99.5%), respectively.

Park and colleagues (29) assessed a deep learning algorithm's diagnostic accuracy in automatically detecting DDH using anteroposterior radiographs. The study included 5076 hip images from patients up to 12 months old with suspected DDH. The deep learning algorithm exhibited a sensitivity of 98.0%, specificity of 98.1%, positive predictive value of 84.5%, and negative predictive value of 99.8%. There was no significant disparity in DDH diagnosis between the algorithm and experienced paediatric radiologists. However, radiologists lacking in paediatric radiology experience had lower sensitivity, specificity, and positive predictive value when compared with the proposed model. Xu et al. carried out another x-ray imaging study to detect DDH, achieving a classification precision of 95% through the usage of 1265 patient images. Mask RCNN was employed for detecting local features (30). Pham et al. created an automated measurement for migration percentage on pelvis radiographs with respect to hip dysplasia using CNN. Several deep learning algorithms were tested, and maximum accuracy of 94.5% was achieved (31).

This study is based on ultrasound images and machine learning for automatic detection of DDH. Automatic detection studies for DDH, based on ultrasound images, are prevalent in the literature with numerous publications supporting the findings of this study. Hu et al. developed a multi-task framework that automated the evaluation of DDH through the use of Mask R-CNN. Their recommended approach yields 93% accuracy in identifying alpha angles below 5 degrees (32). Liu et al. (33) proposed a feature attention network to improve the accuracy of angle measurement for neonatal femur segmentation using ultrasound. The network utilises 400 images obtained from a publicly available dataset, resulting in a reduction of doctors' error rates from 6-10% to 2%. Another related study by Chen et al. presented a deep learning-based computer-aided framework for diagnosing DDH. The framework automatically detects standard planes and measures angles for Graft type I and type II hips. They reported a classification accuracy of 94.71%. Additionally, they explored a standard plane scoring module to calculate the scoring formula and identify the most suitable ultrasound image, which is similar to the proposed study (14).

Huang et al. (34) constructed a network in accordance with the guidelines of the American College of Radiology (ACR) and the American Institute of Ultrasound in Medicine (AIUM). Their goal was to devise an innovative technique for the automatic measurement of ultrasound-based DDH using deep neural networks (DNN).

Based on the findings presented in Table III, our study demonstrates that integrating the model into a real-time decision support system is easily achievable. The model demonstrated outstanding performance with the highest accuracy value of 0.8762. The precision, recall, and F1-score metrics are consistent with this outcome, indicating the reliability of the model. Additionally, the confusion matrix in Figure I shows that the model has an accuracy rate of 89.45% in identifying false images. These results indicate that the likelihood of selecting an incorrect image is only 10.55%.

Well-trained and accurate ultrasound images are crucial in all of these studies. If individuals lack the experience to precisely measure the angles of the images, the diagnosis of DDH may be compromised. The acquisition of reliable and precise images is essential for correctly diagnosing DDH (32, 34). Our goal is to mitigate the issues arising from inaccurate image acquisition and evaluation. We assume that it is possible to help less experienced people by

defining what is true and false of the image. This problem is our motivation to carry out this study using 3600 photographs taken from 100 subjects. In this study, 8 different machine learning algorithms were used to develop the correct image decision-making support system.

The study has limitations, notably a small sample size. Further research with a larger sample size is required to enable generalization of the results. Additionally, our study did not employ the Graf classification system, precluding knowledge of the sample types according to Graf. This is an important consideration for treatment decisions. Although the determination of measurement points is a matter of physician experience, in our study there were no reference points that could not be determined due to image quality and baby age. The effect of the ultrasound machine used, the image quality and the baby's age on the clinician's ultrasound scan can be evaluated in future studies.

Conclusion

Machine learning algorithms are capable of evaluating ultrasound images for the diagnosis of developmental dysplasia of the hip (DDH). Early-stage diagnostic accuracy can be enhanced through the identification of appropriate images by physicians. Furthermore, the integration of machine learning into ultrasound devices may reduce the occurrence of false evaluations in DDH diagnosis.

Our study also offers valuable insights into diagnostic approaches by demonstrating the potential of artificial intelligence to differentiate between normal hip cases and DDH cases without the need for angle measurements in ultrasound images.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Prediction of Myometrial Invasion Depth and Staging in Endometrial Cancer Patients with Three-Dimensional Ultrasonography Using VOCAL Technique: A Prospective Study

Endometrium Kanseri Hastalarında 3D Ultrasonografi VOCAL Teknikle Myometriyal İnvazyon Derinliği ve Evre Prediksiyonu: Prospektif Çalışma

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1388759
Geliş Tarihi | Received: 10.11.2023
Kabul Tarihi | Accepted: 17.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Işık G, Mutlu Sütçüoğlu B, Soykan Y, Kazancı F, Erdem Ö, Onan MA. Prediction of Myometrial Invasion Depth and Staging in Endometrial Cancer Patients with Three-Dimensional Ultrasonography Using VOCAL Technique: A Prospective Study. Hitit Medical Journal 2025;7(1):88-94. https://doi.org/10.52827/hititmedj.1388759

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Bu çalışma için Gazi Üniversitesi Klinik Araştırmalar Etik Kurulu tarafından onay alınmıştır. (Karar No: 2018-836)
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: GI, BMS, MAO; Tasarım: GI, BMS, YS, FK, MAO; Veri Toplama/Veri İşleme: GI, BMS, YS, FK, MAO; Veri Analizi: GI,BMS,OE Makalenin Hazırlanması: GI, BMS, YS, FK, OE, MAO.
Hasta Onamı: Her hastaya çalışma hakkında detaylı bilgi verilmiş olup, çalışmaya katılmayı kabul eden hastalardan yazılı ve sözel olarak onam alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: This study was approved by the Gazi University Clinical Research Ethics Committee. (Decision no: 2018-836)
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: GI, BMS, MAO Design: GI, BMS, YS, FK, MAO Data Collection/Data Processing: GI, BMS, YS, FK, MAO Data Analysis: GI, BMS, OE Manuscript Preparation: GI, BMS, YS, FK, OE, MAO.
Informed Consent: Detailed information about the study was provided to each patient, and written and verbal informed consent was obtained from those who agreed to participate.
Financial Disclosure: There are no financial funds for this article.

Prediction of Myometrial Invasion Depth and Staging in Endometrial Cancer Patients with Three-Dimensional Ultrasonography Using VOCAL Technique: A Prospective Study

ABSTRACT

Objective: In this study, the aim was to compare preoperative endometrial volume measurements using three-dimensional transvaginal ultrasonography in cases of endometrioid type endometrial cancer with both intraoperative frozen results and final pathology results.

Material and Method: Ultrasonography was performed using a GE Voluson E6 ultrasound device with a three-dimensional transvaginal probe immediately before surgery for all endometrial cancer patients who had endometrial biopsy results of the endometrioid type. Endometrial volume measurement was calculated in cm^3 using the VOCAL method for uterine total volume measurement, and drawings were made for endometrial thickness and disease-free myometrial volumes. Volume measurements were prospectively recorded along with frozen and final pathology results.

Results: A total of 50 patients were included in the study. There was no statistically significant difference between three-dimensional transvaginal ultrasonography measurements of endometrium, myometrium, and uterine volumes when myometrial invasion was less than or greater than 50% (*p=0.3, p=0.3, p=0.6*, respectively). Similarly, no statistically significant difference was found in the ratio of endometrial volume to uterine volume when evaluating myometrial invasion below and above 50% (*p=0.21*).

Conclusion: While three-dimensional transvaginal ultrasonography offers the possibility of three-dimensional volume measurement of the uterus and holds promise for predicting myometrial infiltration, our study has shown that it is still a technique that requires further investigation. More research is needed to assess its usability in the context of endometrial cancer invasion.

Keywords: Endometrial cancer, predictiveness, prognosis, three-dimensional ultrasonography, ultrasonography.

ÖZET

Amaç: Bu çalışmada, endometrioid tip endometrium kanserli vakaların üç boyutlu – transvajinal ultrasonografi ile preoperatif endometrial volüm ölçümlerinin hem intraoperatif frozen sonuçları hem de nihai patoloji sonuçları ile karşılaştırılması hedeflenmiştir.

Gereç ve Yöntem: ÇEndometrial biyopsi sonuçları endometrioid tip gelen, operasyon için hospitalize edilen tüm endometrium kanseri hastalarına operasyondan hemen önce GE Voluson E6 ultrasonografi cihazı ile üç boyutlu transvajinal probu kullanılarak ultrasonografi yapıldı. Endometrial volüm ölçümü, uterin total volüm ölçümü VOCAL yöntemi kullanılarak; endometrium kalınlığı ve hastalıksız myometrium volümleri çizim yapılarak cm^3 olarak hesaplandı. Volüm ölçümleri, frozen ve nihai patoloji sonuçları prospektif olarak kaydedildi.

Bulgular: Çalışmaya toplam 50 hasta dâhil edildi. Myometerium invazyonunun %50'den az ya da çok olması ile, üç boyutlu – transvajinal ultrasonografi ile yapılan endometrium, myometrium ve uterus volüm ölçümleri arasında istatistiksel anlamlı fark saptanmamıştır (sırasıyla *p=0,3, p=0,3, p=0,6*). Endometrium volümünün uterus volümüne oranı değerlendirildiğinde yine myometrial invazyon %50 altında ve üzerinde olan gruplarda istatistiksel anlamlı fark saptanmamıştır (*p=0,21*).

Sonuç: Üç boyutlu – transvajinal ultrasonografi uterusun üç boyutlu volüm ölçümüne olanak sağladığından, myometrial infiltrasyon prediksiyonunda umut vaadedici olsa da, çalışmamızın sonucu da göstermiştir ki halen araştırılması gereken bir tekniktir. Endometrial kanser invazyonu açısından kullanılabilirliğini ölçebilmek adına daha çok çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Endometrium kanseri, prediktivite, prognoz, ultasonografi, üç boyutlu ultrasonografi.

Giriş

Endometrium kanseri kadınlarda görülen en sık pelvik kanserdir (1). Tedavide FIGO (International Federation of Gynecology and Obstetrics) kriterlerine göre cerrahi evreleme ve buna göre total histerektomi, salpingooferektomi ve batın yıkama sıvısından sitolojik çalışma yapılması rutindir. Ancak düşük riskli grupta lenfadenektomi yapılması tartışmalı konulardan biridir (2). Prognozu etkileyen en önemli faktörler FIGO evresi, myometrial infiltrasyon, histolojik tip ve tümör grade'i olarak bilinmektedir. Myometrial infiltrasyonun % 50'den fazla olması hem pelvik lenf nodu metastazı hem de parametriyal yayılım açısından önemlidir ve surveyi tek başına belirleyen en önemli faktördür (3). Myometrial invazyonun bilinmesi; operasyon öncesi düşük ve yüksek risk ayrımının yapılmasına, operasyon planının çizilmesine ve gerekli olmayan bir lenfadenektomiden kaçınılmasına olanak sağlayabilir.

Myometrial infiltrasyonun belirlenmesinde transvajinal ultrasonografinin (TVUSG) kullanımı ilk defa 1989 yılında bildirilmiş ve bu tarihten itibaren konuyla ilgili araştırmalar çoğalmıştır (4). Gelişen teknoloji ile birlikte de üç boyutlu transvajinal sonografinin (3D – TVUSG) kullanıma girmesi konuya daha ciddi bir bakış açısı sağlamıştır. 3D - TVUSG'nin ölçümlere pek çok dikey eksen eklemesi sayesinde daha kesin volüm ölçümleri sağlanabilmektedir. Bilgisayar destekli VOCAL (virtual organ computer-aided analysis, VOCAL™) programı sayesinde ise rotasyonel volümetrik ölçümler ile dokunun üç boyutlu hacim hesabı yapılabilmektedir. Yakın zamanda yapılmış tek bir prospektif çalışmada myometrial invazyonun tespitinde %88 spesifite, %100 sensitivite ve %100 negatif prediktif oran ile endometrial kanser vakalarında 3D-TVUSG kullanılabileceği bildirilmiştir (5). Literatürde bu alanda yapılan çalışma sayısının sınırlı olması nedeniyle 3D-TVUSG henüz rutin pratikte kullanıma girememiş olup, bu konuda ek çalışmalara ihtiyaç vardır.

Biz de mevcut çalışmamızda prospektif olarak, en sık görülen histopatolojik alt tip olan endometrioid tip endometrium kanserli vakaların 3D – TVUSG ile preoperatif endometrial volüm ölçümlerinin hem intraoperatif frozen sonuçları hem de nihai patoloji sonuçları ile korelasyonunu karşılaştırmayı hedefledik.

Gereç ve Yöntem

Çalışmaya etik kurul onayı alındıktan sonra başlandı. 2017-2019 yılları arasında tersiyer merkezde kadın hastalıkları ve doğum kliniğine başvurmuş, endometrial biyopsi sonuçları endometrioid tip endometrium kanseri grade 1 ve grade 2 olarak raporlanan 50 hasta dâhil edildi. Grade 3 endometrioid tip kanserler ve diğer histolojik tip endometrium kanserleri çalışmaya dâhil edilmedi.

Bu prospektif çalışma, endometrial biyopsi sonuçları endometrioid tip olarak bildirilen ve cerrahi müdahale planlanan endometrium kanseri tanılı hastalarda, üç boyutlu transvajinal ultrasonografi (3D-TVUSG) kullanılarak yapılan preoperatif endometrial hacim ölçümlerinin intraoperatif frozen sonuçları ve nihai patoloji sonuçları ile korelasyonunu değerlendirmeyi amaçlamaktadır. Çalışma, 2017-2019 yılları arasında, tersiyer bir sağlık merkezinin kadın hastalıkları ve doğum kliniğine başvuran 50 hasta üzerinde gerçekleştirilmiştir. Bu çalışma için ilgili etik kurul onayı alınmıştır.

Hasta Seçimi

Çalışmaya yalnızca endometrioid tip endometrium kanseri tanısı alan grade 1 ve grade 2 hastalar dahil edilmiştir. Grade 3 endometrioid kanserler ve diğer histolojik tip endometrium kanserleri çalışma kapsamı dışında bırakılmıştır.

Görüntüleme Protokolü

Operasyondan hemen önce, tüm hastalara GE Voluson E6 ultrasonografi cihazı kullanılarak 3D transvajinal prob ile görüntüleme yapılmıştır. Bu görüntüleme sırasında 2D modda endometrial kalınlık (mm) ve tümöral infiltrasyon gözlemlenmeyen myometrium kalınlıkları ölçülmüştür. Endometrial volüm hesaplamaları, uterin toplam volüm ölçümleri için VOCAL (Virtual Organ Computer-aided AnaLysis) yöntemi kullanılarak yapılmıştır. VOCAL yöntemi, 30° rotasyon açısıyla yapılarak toplamda 6 kesit kullanılarak gerçekleştirilmiştir. Bu işlem sırasında, endometrium ve hastalıksız myometrium volümleri manuel çizimler yapılarak ölçüm yapılmıştır. Ölçümler cm^3 cinsinden kaydedilmiştir.

Cerrahi Protokol ve Frozen İncelemesi

Görüntüleme işlemleri tamamlandıktan sonra hastalar, deneyimli bir jinekolojik onkoloji cerrahi ekibi tarafından opere edilmiştir. Preoperatif dönemde 3D-TVUSG sonuçları cerrahi ekibe sunulmamıştır.

Standart cerrahi evreleme protokolüne göre tüm hastalarda intraoperatif frozen kesitler alınmış ve patolojik değerlendirmeleri yapılmıştır. Cerrahi sonrasında elde edilen frozen sonuçları ile nihai patoloji sonuçları, tek merkezde ve aynı patoloji ekibi tarafından değerlendirilen spesmenler üzerinden karşılaştırılmıştır.

Veri Toplama ve Analiz

Tüm ultrasonografi ve cerrahi işlemler, 3D TVUSG deneyimi olan tek bir jinekolog onkolog tarafından gerçekleştirilmiş, böylece ölçümler arası subjektif farklar minimize edilmiştir. Patolojik spesimenlerin değerlendirilmesi sırasında, myometrial invazyon derinliği, endometrial kalınlık, myometrial ve uterin volümler gibi parametreler prospektif olarak kayıt altına alınmıştır.

İstatistiksel Analiz

Veriler SPSS version 22 kullanılarak analiz edilmiştir. Verilerin normal dağılıma uygunluğu "Kolmogorov-Smirnov" ve "Shapiro-Wilk" testi kullanılmıştır. Normal dağılıma uyan veriler için ortalama ± standart sapma, normal dağılıma uymayan veriler için ortanca ile 25. ve 75. Persentil değerleri kullanılmıştır, kategorik veriler yüzde (%) olarak verilmiştir. Kategorik değişkenlerin karşılaştırılması "Chi-Square Test" kullanılarak yapılmıştır. Bağımsız gruplar arasında normal dağılıma uymayan sayısal iki grup verilerinin karşılaştırılmasında "Mann Whitney U Test" kullanılmıştır. Normal dağılıma uymayan sayısal verilerin korelasyonunda Spearman korelasyon testi kullanılmıştır. 3D TVUSG ölçümlerinin nihai patoloji sonuçlarını öngörmede tanısal karar verdirici özellikleri ROC eğrisi analizi ile incelenmiştir. Değerler arası uyumun güvenilirliğini tespit edebilmek için "Cohen Test" kullanılmıştır.

Bulgular

Endometrioid tip endometrium kanseri tanılı toplam 50 hastaya kliniğine, evresine, tümör derecesine göre cerrahi yapıldı. Çalışmaya dâhil edilen hastaların yaşlarının ortalaması ve standart sapmaları sırasıyla 60,9±8,7, vücut kitle indeksi ortalaması 33,1±7,2 (kg/cm^2) idi. Hastaların karakteristik özellikleri Tablo I'de verilmiştir.

Tüm hasta grubunda endometrium kalınlığın TVUSG ile ölçülen median değeri 13 mm (min-max:0-41) olarak saptandı. Tüm hasta grubunda TVUSG ile ölçülen uterus boyutları 40 mm (min-max:21-76) mm olarak hesaplandı. Yapılan sonografik vaskülarizasyon ölçümlerinde hastaların 22 hastada (%44) hiç kanlanma izlenmemiş, 8 hastada (%16) tek damarlanma, 11 hastada (%22) multiple damarlanma ve 9 hastada (%18) dallanan damar yapısı olduğu görülmüştür. Hastaların 3D olarak volümetrik ölçümleri değerlendirildiğinde median endometrium volümü 6,1 cm^3 (min-max: 0,3-78) olarak hesaplandı. Uterus volümü ise median 62 cm^3 (min-max: 20-411) olarak bulunmuştur. Uterin volümün endometrium volümüne oranının medianı 9 (min-max: 0,5-72) olarak tespit edilmiştir.

Tablo I. Hastaların Karakteristik Özellikleri

	n	%
Kanlanma		
Yok	22	%44
Tek	8	%16
Multiple	11	%22
Dallanan	9	%18
Operasyon		
TLH, BSO	29	%58
TAH, BSO	9	%18
TLH, BSO, PLND	2	%4
TAH, BSO, PPLND, Omentektomi	10	%20
Frozen		
İnvazyon Yok	9	%18
Yüzeyel	10	%20
1/3 İnvazyon	4	%8
1/2 'den Az İnvazyon	16	%32
½'den Fazla İnvazyon	11	%22
Nihai Patoloji		
%50'den Az	38	%76
%50'den Fazla	12	%24

Tüm hasta grubunda patolojik myometrial invazyon yüzdesinin medianı %25 (min-max: 0-100) olarak saptanmıştır. Nihai patolojide myometrial invazyonu %50'nin altında olan 38 hasta (%76) ve %50'nin üzerinde olan 12 hasta (%24) olduğu saptanmıştır. Nihai patoloji ile frozen uyumuna bakıldığında, tüm hastalarda genel uyum değerlendirildiğinde 50 hastanın 45'inde nihai patoloji ve frozen sonuçları uyumlu izlendi (%90, $p<0.001$, kappa değeri 0,805, mükemmel uyum).

Tablo II. 3D USG Volüm Ölçümlerin Nihai Endometrial İnvazyon ile İlişkisi

3D USG Volüm Ölçümleri	Nihai Patoloji İnvazyon Yüzdesi < %50		Nihai Patoloji İnvazyon Yüzdesi >%50		
	Median	Min-Max	Median	Min-Max	p değeri
Endometrium	6	0,3-78,2	6,9	1,3-47,6	0.33
Myometrium	14,4	5-29,5	11,9	4-38	0.32
Uterus	63	20-411	62,3	18,8-159,8	0.61
Endometrium/ Uterus	8,1	0,5-72,3	21,3	2-37,5	0.21

Endometriumun 3D volümetrik ölçüm sonuçları ile myometrial invazyon derecesinin korelasyonu değerlendirildiğinde istatistiksel anlamlı fark saptanmış, pozitif yönde yüksek düzeyde korelasyon olduğu tespit edilmiştir (*p=0.04, r=0.77*). Uterus ve myometrial volüm ölçümleri ile patolojik myometrium invazyon derecesi arasındaki korelasyon değerlendirildiğinde istatistiksel anlamlı fark saptanamamıştır (*p>0.2 ve p>0.5*). 3D-USG'de endometrium volümü için bir cut-off değerinin, %50 den fazla myometerium invazyonunu tahmin etmedeki etkinliğinin değerlendirilmesi için ROC analizi yapıldı. ROC analizinde yeterli sensitivite ve spesifiteye ait bir değer saptanmadı. Bu nedenle, endometrium volümü 3D USG sonuçlarının medianına göre hastalar iki gruba ayrıldı. Endometrium volümü düşük olan grup ile yüksek olan grup arasında myometrium invazyonu arasında ilişki saptanmadı (*p=0.42*)

Myometrial invazyonu derecesi <%50 ve >%50 invazyon olan hastaların sonuçlarını ayrı ayrı değerlendirilmiştir. Myometerium invazyonunun % 50'den az ya da çok olması ile, 3D-USG ile yapılan endometrium, myometrium ve uterus volüm ölçümleri arasında istatistiksel anlamlı fark saptanmamıştır (sırasıyla *p=0.3, p=0.3, p=0.6*). Endometrium volümünün uterus volümüne oranı değerlendirildiğinde yine myometrial invazyon %50 altında ve üzerinde olan gruplarda istatistiksel anlamlı fark saptanmamıştır (*p=0.21*) (Tablo II).

Tartışma

Endometrium kanserinde lenfadenektomi tedavi ve evreleme için en önemli prosedür olmakla birlikte erken evre endometrium kanserinde sağ kalım üzerine belirgin etkisi olmadığı uzun zamandır bilinmektedir (6). Diğer taraftan lenf nodu metastazı 5 yıllık hastalıksız sağ kalımı %80-90 dan %54'e düşürmektedir. Düşük gradeli endometrium kanserinde myometrial invazyon %50'nin üzerine çıktığı durumlarda lenf nodu metastaz riski %4'ten %15'e çıkmaktadır (7). Bu nedenle myometrial invazyon erken evrede lenf nodu metastazı için en önemli risk faktörüdür. Myometrial invazyon derinliğinin belirlenmesinde altın standart histopatolojik tanı olmakla birlikte preoperatif manyetik rezonans (MRI) görüntüleme ve transvajinal ultrasonografi (TV-USG) ile myometrial invazyon prediksiyonu mümkündür (8). MRI invazyon derinliğini %83 sensitivite ve %93 spesifite ile doğru olarak belirleyebilmektedir (9). TV-USG'nin sensitivitesi ise %75 daha düşük olarak izlenmekte iken spesifitesi %86 olarak bulunmuştur (10). Diğer bir çalışmada TV-USG myometrial invazyon yakalama sensitivitesi %68,4 olarak daha düşük hesaplanmıştır (11). Myometrium ve endometrium arasındaki bileşkeyi ayırmak çoğunlukla kolay olsa da ikisi arasındaki herhangi bir kesitteki düzensizlikleri izlemek zor olabilir ve myometrial invazyon tahminlerini yanıltabilir (12). 3D ultrasonografi ise myometriumu birçok kesiti ile değerlendirebilir; bu sayede myometrial invazyon daha doğru değerlendirilebilir (5).

Literatürde yapılan çalışmaların büyük çoğunluğunda MRI ile myometrial invazyon derinliği değerlendirme sonuçlarının tanısal doğruluğu 2D ve 3D TV-USG ölçümlerine göre daha yüksek bulunmuştur (13, 14). Örneğin, Torricelli ve arkadaşları, MRI ile yapılan ölçümlerin %83 sensitivite ve %93 spesifiteye sahip olduğunu göstermiştir (9). Buna karşın, TVUSG'nin sensitivitesi %75 gibi daha düşük bir seviyede kalırken, spesifitesi %86 olarak hesaplanmıştır. Bu çalışmaların aksine Yıldırım ve arkadaşlarının 2018 yılında yayınladığı sonuçlarda 3D TV-USG ile myometrial invazyon derinliğini MR'dan da daha iyi tahmin edebilme şansı olduğunu göstermektedir. MRI'dan daha kolay, ucuz ve etkili bir görüntüleme yöntemi olarak izlenmiştir (8). Bu çalışmada hedefimiz; maliyeti minimale indirecek şekilde, MRI uygulaması yapılmaksızın rutin yapılan TV-USG ile doğru evreleme yapıp operasyonu yönlendirmektir.

Stachowiak ve arkadaşlarının yaptığı başka bir çalışmada, grade 2 endometrium kanseri hastalarında 3D ultrasonografi ile yüksek endometrial volüm ölçümleri gözlemlenmiş ve bu bulgular anlamlı bulunmuştur; ancak grade 1 vakalar kontrol grubuyla karşılaştırıldığında anlamlı bir fark saptanmamıştır (15).

Çalışmamızda grade 1 endometrium kanseri hastaları çoğunlukta olup volüm ölçümünün istatistiksel olarak anlamlı sonuçlar vermemesi literatürle bu açıdan da uyumludur. Çalışmamızın bir kısıtlılığı kontrol grubu olmaması ve volüm ölçümlerinin kontrol grubu ile karşılaştırılamaması olarak kabul edilebilir. Diğer yandan 3D USG evreleme prediksiyonunda yararlı bir yöntem olmakla birlikte subjektif bir tanı yöntemidir. Myometrial invazyon derinliğinin objektif olarak tahmin edilmesi için 3D-TVUSG'nin objektif yapılması gerekmektedir ve bunun için 3D-TVUSG öğrenme eğrisi standardize edilmelidir; bu şekilde test performansı arttırılabilir (16). Bizim çalışmamız literatürle uyumlu şekilde operasyon sırasındaki frozen sonucunun myometrial invazyon derinliğine göre operasyonun şeklinin belirlenmesi, lenfadenektomi kararı verilmesi açısından standart prosedür olduğunu göstermektedir.

Görüntüleme yöntemleri ile myometrial invazyonu değerlendirmek cerrahi planı için yardımcı olur. Ancak çalışma sonuçlarımız deneyimli 2D USG ile evreleme prediksiyonu yeterliliğini göstermektedir. 3D USG volüm ölçümleri ile 3D volüm ölçümlerinde prediksiyon için cut-off değer belirlemek önemlidir. Bu nedenle daha fazla sayıda hastada 3D TVUSG uygulaması gereklidir. Ancak cut-off belirlenmesi halinde bile ultrasonografi subjektif bir test olarak değerlendirmektedir; bu nedenle ultrasonografinin deneyimli klinisyen tarafından uygulanması önemlidir. Ergenoglu ve arkadaşlarının çalışması ise, 3D-TVUSG'nin, myometrial invazyonu öngörmede subjektif ölçüm hatalarını azaltabilmek için belirli bir öğrenme eğrisine ihtiyaç duyduğunu belirtmektedir (17). Yang ve arkadaşlarının 2019'da yaptığı çalışmada MRI ve 3D-USG kombine edildiğinde myometrial invazyon ve servikal invazyon prediksiyonlarının sensitivitesinin arttığını, spesifitesinin azaldığını göstermiştir. Çalışmada sensitivitedeki artış operasyon şeklinin ve endometrium kanseri cerrahisinin kişiselleştirilebileceğini belirtmektedir. Bunun yanı sıra 3D- USG ile lenf nodu metastazı prediksiyonu yapılamamaktadır. Çalışmamızda maliyet azalması amacı ile MRI ölçümleri yapılmamıştır; ancak Yang ve arkadaşlarının çalışması tek başına 3D USG ölçümlerinden ziyade USG'nin MRI görüntüleme ile kombine edilerek cerrahi planı kişiselleştirilebileceğini göstermektedir (18).

Hasta sayısının azlığı çalışmamızın kısıtlılıkları arasında yer almaktadır. Ek olarak randomize bir çalışma olmaması nedeniyle hasta yaşlarının benzer olmaması çalışmanın bir limitasyonu olarak gösterilebilir. Ek olarak küretaj öncesi ölçümler yapılamamış olup, küretaj öncesi ölçümler ile çalışma sonuçları arasındaki ilişkinin irdeleneceği çalışmalar yol gösterici olabilir. USG'nin tek klinisyen ve operayonların tek ekip tarafınca yapılmasının subjektif farklılıkları en aza indirdiği düşünülmektedir. Özellikle 3D-TVUSG ve MRI gibi yöntemlerin kombine kullanımı, bazı çalışmalarda invazyon tespiti açısından avantaj sağlamıştır. TVUSG'de volüm ölçümleri ve oranlarının evre belirlemesi amacı ile kullanılması için cut-off değerler belirlenmelidir. Bu amaçla hasta sayısının arttırıldığı çalışmalar ve normal endometrium ve myometrium volümlerinin normal dağılımlarının değerlendirilebileceği yeni çalışmalar planlanabilir. Sonuçta 3D TVUSG uterusun üç boyutlu volüm ölçümüne olanak sağladığından, myometrial infiltrasyon prediksiyonunda umut vaadedici olsa da, çalışmamızın sonucu da göstermiştir ki halen araştırılması gereken bir tekniktir. Endometrial kanser invazyonu açısından kullanılabilirliğini ölçebilmek adına daha çok çalışmaya ihtiyaç vardır.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Is Pulsed Radiofrequency of C2 Dorsal Root Ganglion an Option for Tinnitus Treatment?

C2 Dorsal Kök Gangliyonuna Pulse Radyofrekansı Tinnitus Tedavisinde Bir Seçenek Midir?

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1541358
Geliş Tarihi | Received: 02.09.2024
Kabul Tarihi | Accepted: 27.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Kurçaloğlu M, Kavaz Uştu E, Yaşar C, et al. Is Pulsed Radiofrequency of C2 Dorsal Root Ganglion an Option for Tinnitus Treatment? Hitit Medical Journal 2025;7(1):95-100. https://doi.org/10.52827/hititmedj.1541358

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Çalışma için 17/01/2024 tarihinde Ondokuz Mayıs Üniversitesi Klinik Araştırmalar Etik Kurulu'ndan onay alınmıştır. Karar no: 2024/12.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Tasarım: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Veri Toplama/Veri İşleme: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Veri Analizi: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Makalenin Hazırlanması: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG.
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: : Approval for the study was obtained from the Ondokuz Mayıs University Clinical Research Ethics Committee on 17/01/2024. Decision no: 2024/12.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Design: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Data Collection/Data Processing: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Data Analysis: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG Manuscript Preparation: MK, EKU, CY, FY, PUU, AD, SÇK, ÖK, FÖ, FG.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Is Pulsed Radiofrequency of C2 Dorsal Root Ganglion an Option for Tinnitus Treatment?

ABSTRACT

Objective: Tinnitus is a chronic problem with low treatment success. Pulsed radiofrequency application (PRF) to the second cervical dorsal root ganglion (C2 DRG) has been suggested as a possible treatment for tinnitus. This study aimed to evaluate the effectiveness of C2 DRG PRF for tinnitus.

Material and Method: Patients who underwent C2 DRG PRF treatment due to chronic tinnitus were included in this retrospective study. PRF was performed using a 5 cm length with a 5 mm active tip RF electrode for 4 minutes under a C-arm fluoroscopic view. The Tinnitus Handicap Inventory (THI) was applied before and one month after the procedure. Significant symptom relief was regarded as a 50% decrease in THI scores at a one-month check-up visit.

Results: A total of 22 patients were included in the study. Mean THI scores before, and one month after the procedure were 42.36±25.43 and 37.31±25.04, respectively (*p=0.28*). Only one patient (4.5%) had significant symptom relief (*p=0.31*).

Conclusion: Based on the results of this study, we suggest that PRF of C2 DRG is not an effective and reliable method for chronic tinnitus treatment. Further studies using different interventional techniques and large patient groups may be helpful in the treatment of this persistent complaint.

Keywords: Dorsal root ganglion, hearing loss, radiofrequency, tinnitus.

ÖZET

Amaç: Tinnitus, düşük tedavi başarı oranına sahip, kronik bir hastalıktır. İkinci servikal dorsal kök gangliyonuna (C2 DRG) uygulanan pulse radyofrekansın (PRF) muhtemel bir tedavi yöntemi olduğu öne sürülmüştür. Bu çalışmanın amacı, C2 DRG PRF'in tinnitus tedavisinde olan etkinliğini değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya kronik tinnitus nedeniyle C2 DRG PRF uygulanmış olan hastalar dahil edildi. PRF, 5 cm uzunluğunda, 5 mm aktif uçlu RF elektroduyla C-kollu skopi görüntülemesiyle 4 dakika süreyle uygulandı. Hastaların işlemden önce ve işlemden bir ay sonraki kontrollerinde uygulanan Tinnitus Handikap Envanteri (THE) skorları değerlendirildi. Birinci ay kontrollerinde THE'de %50 ve fazlası azalma, belirgin semptom azalması kabul edildi.

Bulgular: Toplam 22 hasta çalışmaya dahil edildi. İşlemden önceki ve bir ay sonraki THE skorları sırasıyla 42,36±25,43 ve 37,31±25,04 idi (*p=0.28*). Sadece bir hastada belirgin semptom azalması oldu (*p=0.31*).

Sonuç: Çalışmalarımızın sonuçlarına göre, C2 DRG PRF işleminin tinnitus için etkin ve mâkul bir yöntem değildir. Bu inatçı hastalığın tedavisi için başka girişimsel işlemleri içeren daha fazla hasta sayılarına sahip çalışmalar yardımcı olabilir.

Anahtar Sözcükler: Dorsal kök gangliyonu, işitme kaybı, radyofrekans, tinnitus.

Introduction

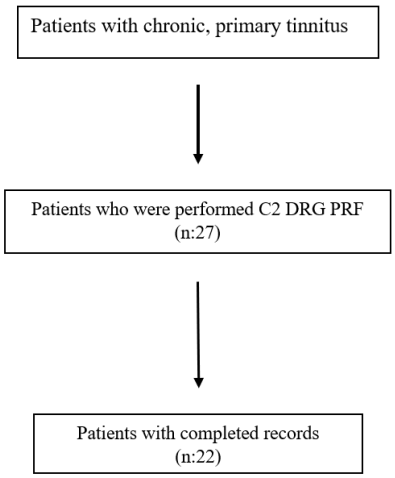
Tinnitus is an auditory symptom characterized by abnormal sounds. It is a common complaint, and the estimated rate of tinnitus is 22% (1). The frequency increases with age and is higher in people older than 65 years (2). Despite almost a quarter of society experiencing tinnitus, only 3-5% of people require treatment (2). The main risk factors for tinnitus are noise exposure, hearing loss, and mental stressors. In subjective tinnitus -which is the frequent form- only the patient hears the abnormal sound in the auditory system, while another person can hear the sound in objective tinnitus. Tinnitus is named 'primary tinnitus' when there is no specific underlying cause and called 'secondary tinnitus' if there is a pre-existing specific etiology (3). Common causes of secondary tinnitus are noise-induced hearing loss, presbycusis, otosclerosis, otitis, impacted cerumen, Meniere's disease, sudden deafness, head or cervical injury, multiple sclerosis, acoustic neuroma, cerebellopontine angle tumors, otitis media, Lyme disease, meningitis, or side effects of some drugs (4). However, in many cases, the cause of tinnitus remains unidentified (5). When the duration of tinnitus is shorter than six months, it is called 'acute tinnitus', and if it is longer than six months, it is called 'chronic tinnitus' (3).

In the literature, there is no strongly effective treatment for tinnitus. Ginkgo biloba extracts, antidepressants, benzodiazepines, zinc, melatonin, cannabis, oxytocin, steroids, and gabapentin are not effective for tinnitus treatment (2). Pulsed radiofrequency (PRF) of the second cervical dorsal root ganglion (C2 DRG) under C-arm fluoroscopy is an interventional pain medicine procedure, and it was shown to be effective for the treatment of headache in several studies (6,7). Furthermore, Koning and Haasnoot suggested that C2 DRG PRF has beneficial effects for tinnitus treatment (8,9). In their study with 61 patients, Koning et al. reported symptom relief in 25% of patients, and they also reported that symptom relief was maintained in half of these patients 13 months later (8). The primary aim of this retrospective study was to assess the efficacy of PRF treatment of C2 DRG under C-arm fluoroscopic imaging in patients with chronic tinnitus. The secondary aim was to observe possible complications or side effects developed due to the intervention.

Material and Methods

This retrospective study was conducted in Ondokuz Mayıs University Faculty of Medicine, Anesthesiology and Reanimation Department, Pain Clinic. Ethical approval was obtained from the institutional ethics committee (Decision number: OMUKAEK 2024/12). Patients who underwent C2 DRG PRF due to chronic primary tinnitus complaints between January 2021 and November 2023 were included in the study. Patients with tinnitus due to a diagnosed disease, e.g., otitis, Meniere's disease, head or cervical injury, and patients who applied an interventional treatment for tinnitus in the last three months were not included in the study. Patients with cervical facet joint and temporomandibular joint tenderness detected in the physical examination were also not included. Written informed consent was obtained from the patients before the procedures. The Tinnitus Handicap Inventory (THI) was used as the assessment tool. Age, accompanying hearing loss (determined by audiometry test), the affected side(s), and the current medical treatment for tinnitus were recorded. THI scores were recorded before and one month after the intervention. Effective results were determined as 50% reduction in the THI scores.

Table I. Flowchart of patient selection for the study



The C2 DRG PRF procedures in our clinic are performed with the following routine:

The procedures are performed in the operating room of the pain clinic. Cardiac and respiratory

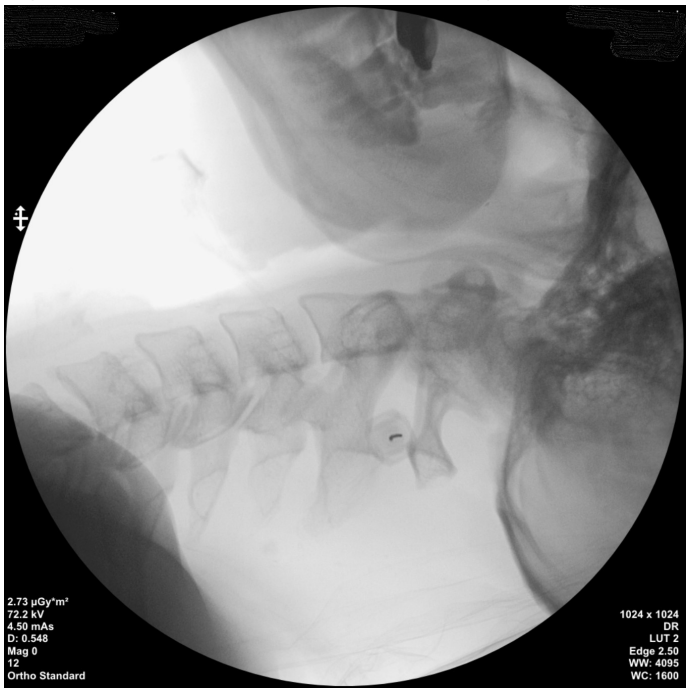
monitorization was performed in all perioperative periods. An intravenous cannula is inserted, and light sedation (1 mg midazolam) is administered in all patients. Patients are placed on the operation table in the supine position, and the area of needle entry is cleaned with povidone-iodine solution. The area is covered with sterile cloths. In a lateral fluoroscopic view, a radiofrequency needle with a 5 cm length and 5 mm active tip (Apro Korea®, Rep. of Korea) is inserted at the six o-clock point of the imaginary circle between the spinous processes of C1 and C2 vertebrae (Figure I). The needle is advanced using the tunnel vision technique. After a few centimeters, the C-arm is positioned in the anteroposterior plane, and the needle is advanced until the lateral border of the facet column (Figure II). Then, sensorial stimulation with 50 Hz is applied by the RF needle, and patients are asked about paresthesia of the neck and posterior part of the head at 0.4 mV, or lower stimulation level. When it is concluded that the needle tip is at the correct location, 4 minutes of PRF (2 Hz) is applied. The voltage of the PRF is dynamically adjusted as long as the patient does not feel disturbance and the temperature does not exceed 42 °C.

Table II. Characteristics of the study population

	n:22
Mean Age	53.22 ± 13.05 years
Female / Male	9 /13 (40.9% vs 59.1%)
Mean duration of complaint	45.59 ± 65.59 months
Right ear affected	5 (22.7%)
Left ear affected	14 (63.6%)
Both ears affected	3 (13.6%)
Accompanying hearing loss	7 (31.8%)

Statistical Package for the Social Sciences version 22 (SPSS 22, IBM Software®, New York, USA) was used for statistical analysis. Nominal data are described by means and standard deviations, while ordinal data are described by numbers and percentages. The Wilcoxon signed-rank test was used to compare the pre-interventional and post-interventional THI scores, and chi-square was used to assess the number of patients with symptom relief following the procedure. P values smaller than 0.05 were regarded as 'statistically significant'.

Figure I. Lateral view of the radiofrequency needle



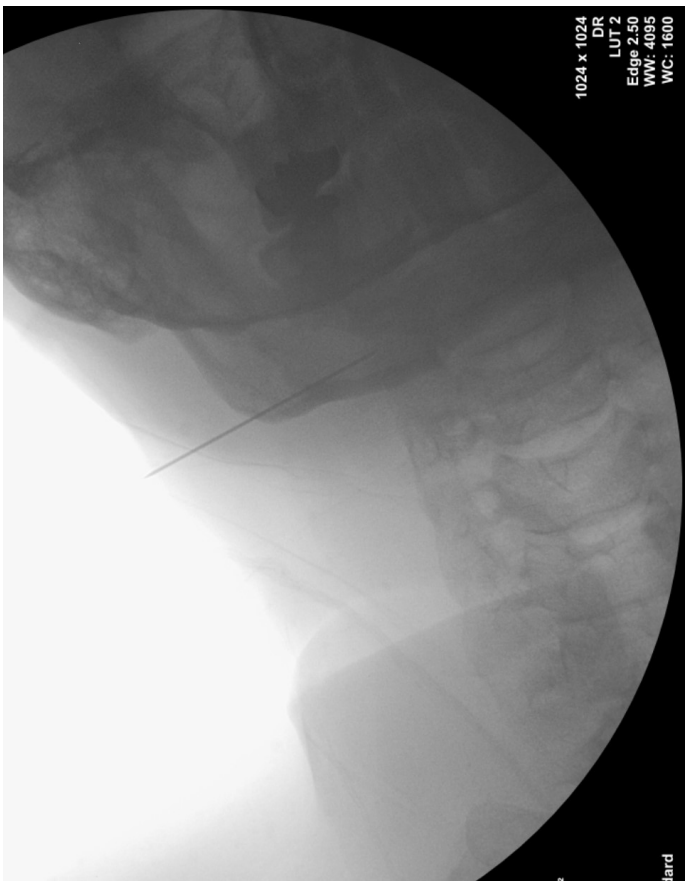
Results

There were 27 patients who underwent C2 DRG pulsed radiofrequency treatment for tinnitus treatment during the related time interval (Table I). Five of them were not included in the study due to the lack of check-up results. A total of 22 patients were included in this study. While 9 (40.9%) of them were female, 13 (59.1%) were male. The mean age of the study population was 53.22 ± 13.05 years. The mean duration of the tinnitus complaint was 45.59 ± 65.59 months (Table II). The right ear was affected in 5 (22.7%), the left was affected in 14 (63.6%), and both ears were affected in 3 (13.6%) patients. Hearing loss was found in 7 (31.8%) patients, and hearing loss was not observed in 15 (68.2%) patients (Table II). Patients with hearing loss had a sensorineural type.

Table III. Results of THI score and rate of patients with significant symptom relief

	Before the Intervention	One month after the intervention	*p value*
Tinnitus Handicap Inventory Score	42.36 ± 25.43	37.31± 50.79	*0.28*
Rate of patients with significant symptom relief	-	1/22	*0.31*

Figure II. A-P view of the radiofrequency needle



Seventeen (77.2%) of the patients were actively using betahistine for tinnitus treatment, and 5 (22.7%) had stopped using any kind of drug for tinnitus treatment due to lack of effectiveness. The mean THI score before the intervention was 42.36 ± 25.43, and it was 37.31± 50.79 one month after the intervention (Table III). There was no statistically significant difference in terms of THI score before and one month after the intervention (*p=0.28*) (Table III). Only one female received significant relief after the intervention. Her preintervention THI score was 96, and she reported that her complaints were totally gone (THI score was zero). There was no statistically significant difference in terms of the number of patients who had significant relief of complaints (*p=0.31*) (Table III). No remarkable side effects were observed due to the intervention.

Discussion

Chronic tinnitus is a complex issue, and treatment options do not provide satisfactory results. Unfortunately, the results of our retrospective study were unsatisfactory. We observed that only one among twenty-two patients had experienced significant symptom relief after the PRF procedure, and there was no significant reduction in mean THI scores. However, our study included only chronic tinnitus patients; therefore, we have no data for the tinnitus patients in the acute period.

There are many studies showing the effective results of C2 DRG RF for headache. It was mainly shown to be effective for cervicogenic headache (6,7).

The clinical application of C2 DRG radiofrequency for the treatment of tinnitus was proposed by a Dutch team. In 2012, Haasnoot et al. presented a case report of someone who suffered from tinnitus for sixteen years and it was almost totally resolved following C2 DRG PRF at 42 °C for 120 seconds (9). Seven years later, Koning, who was one of the authors of the case report above, published an original research paper showing some promising effects on tinnitus treatment (8). They observed that 25% of their 61 patients experienced a decrease in tinnitus intensity in the acute period, and half of these patients still encountered an advantage 13.5 months later.

An interesting point that is different between Koning's study and our study is the clinical characteristics of the study groups. In Koning's study, 67% of the patients had accompanying cervical pain complaints. Koning et al. also found that 87% of the patients who experienced symptom relief with C2 DRG PRF had previous cervical pain complaints. In this retrospective research, none of our patients reported cervical pain either in the examination by the ear-throat-nose department or in pain clinic examination. Based on the combination of the results from Koning's study and this study, it is possible that cervicogenic pain is a positive factor for tinnitus symptom relief with C2 DRG PRF.

Cervical dorsal root ganglion injections, or radiofrequency applications, are complex and advanced interventional pain procedures. Spinal nerve damage, spinal cord damage, intravascular injection, local anesthetic toxicity, hematoma, local infection or meningitis, increased pain, hypoesthesia, allodynia, and loss of strength of the upper extremity are among the possible complications of cervical DRG interventions. Therefore, these interventions must be performed by physicians who have sufficient experience in the interventional pain medicine field.

There are limited numbers of studies suggesting stellate ganglion block or greater occipital nerve block may have beneficial effects on tinnitus (10-12). Due to the retrospective design, this study has some limitations. First of all, this study involved 22 patients. Nevertheless, considering only one patient got symptom relief among 22, it can help to extrapolate some clinical opinions. Secondly, no hearing test results were available one month following the procedure. Therefore, we didn't have the opportunity to investigate the effects of C2 DRG PRF on hearing ability, but the main aim of our study was to assess tinnitus rather than hearing loss. Another limitation was the short duration of follow-up because patients were called for the check-up visit one month after the intervention, and we did not have enough data to project for longer durations.

PRF duration was 4 minutes in this study, and this was based on the personal clinical experience of the pain physicians for the treatment of neck pain or headache. There is no certain consensus on the PRF time for cervical DRG for pain treatment. While some authors use 2 minutes, some authors prefer 4 minutes (13-15). Koning et al. used 2 2-minute duration in the original research on C2 DRG PRF for tinnitus.

In conclusion, chronic tinnitus remains a challenging symptom. Unfortunately, considering the possible complications, the results of this study show that C2 DRG PRF is not an effective and reliable treatment option for chronic tinnitus. Prospective studies, including higher numbers of participants and radiofrequency applications with different parameters, may be helpful for tinnitus treatment.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Staging Gallium-68 DOTATATE PET/CT Imaging in Neuroendocrine Tumors: Relationship between Measured SUVmax of the Primary Tumor and the Pathological Grade and Ki-67 Proliferation Index

Nöroendokrin Tümörlerde Evreleme Galyum-68 Dotatate PET/BT Görüntüleme: Primer Tümör SUVmax Değeri ile Patolojik Grade ve Ki-67 Proliferasyon İndeksi Arasındaki İlişki

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Araştırma Makalesi | Research Article
Doi: https://doi.org/10.52827/hititmedj.1605027
Geliş Tarihi | Received: 21.12.2024
Kabul Tarihi | Accepted: 30.01.2025
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Vural Topuz Ö, Büyüktalancı E. Staging Gallium-68 DOTATATE PET/CT Imaging in Neuroendocrine Tumors: Relationship between Measured SUVmax of the Primary Tumor and the Pathological Grade and Ki-67 Proliferation Index. Hitit Medical Journal 2025;7(1):101-108. https://doi.org/10.52827/hititmedj.1605027

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Bu çalışma Başakşehir Çam ve Sakura Şehir Hastanesi Etik Kurulu tarafından onaylandı (Tarih: Temmuz 2024; Onay numarası: E-96317027-514.10-248465455).
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez:ÖVT,EB Tasarım: ÖVT,EB Veri Toplama/Veri İşleme: ÖVT,EB Veri Analizi: ÖVT,EB Makalenin Hazırlanması: ÖVT,EB
Hasta Onamı: Gerek yok.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: This study was approved by the Ethics Committee of Başakşehir Çam ve Sakura City Hospital (Date: July 2024; Approval number: E-96317027-514.10-248465455).
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: ÖVT,EB Design: ÖVT,EB Data Collection/Data Processing: ÖVT,EB Data Analysis: ÖVT,EB Manuscript Preparation: ÖVT,EB
Informed Consent: Not applicable
Financial Disclosure: There are no financial funds for this article.

Staging Gallium-68 DOTATATE PET/CT Imaging in Neuroendocrine Tumors: Relationship between Measured SUVmax of the Primary Tumor and the Pathological Grade and Ki-67 Proliferation Index

ABSTRACT

Objective: To determine whether the maximum standardized uptake value SUVmax of the primary lesion measured via Ga-68 DOTATATE PET/CT imaging can be used to predict histological grade and Ki-67 proliferation index in treatment-naïve neuroendocrine tumors (NETs).

Material and Method: A total of 57 patients diagnosed with NET who underwent Ga-68 DOTATATE PET/CT between January 2021 and April 2024 were retrospectively evaluated. Patient data including age, histopathology, primary tumor localization, tumor size, Ki-67 proliferation index, histological grade, and SUVmax values from the same tumor were recorded. Histological grades 2 and 3 were pooled into a single group (grade 2&3).

Results: The mean age was 49.44 ± 17.20 years. The most common biopsy locations were the liver (28.07%), stomach (21.05%), and pancreas (19.30%). Median Ki-67 proliferation index was 5 (interquartile range: 2–8). Grade 1 tumors were present in 19 patients (33.33%), grade 2 tumors in 35 patients (61.40%), and grade 3 tumors in 3 patients (5.26%). The SUVmax values were positively correlated with tumor size and Ki-67 proliferation index, and Ki-67 proliferation index was positively correlated with tumor size and mitotic count. Patients with grade 2&3 tumors had significantly higher SUVmax values and were older compared to those with grade 1 tumors. For predicting grade 2&3 tumors, the SUVmax value had an area under the ROC curve value of 0.669 (95% CI: 0.526–0.811, *p=0.039*), which yielded an overall accuracy of 64.91%, with 57.89% sensitivity, 78.95% specificity, 84.62% positive predictive value, and 48.39% negative predictive value, at a cut-off value of >12.5.

Conclusion: Initial Ga-68 DOTATATE PET/CT imaging in NETs demonstrated that the SUVmax value of the primary lesion is positively correlated with Ki-67 proliferation index. A maximum standardized uptake value threshold of >12.5 g/ml was shown to distinguish grade 2&3 tumors at an early stage with high positive predictive value.

Keywords: DOTATATE, NETs, PET, Ga-68, SUVmax.

ÖZET

Amaç: Nöroendokrin tümörlerde (NET) tedavi öncesi Ga-68 DOTATATE PET/BT görüntülemede primer lezyon maximum standartlaştırılmış alım değerinin SUVmax histolojik derece ve Ki-67 proliferasyon indeksini öngörmedeki rolünü belirlemektir.

Gereç ve Yöntem: Ocak 2021-Nisan 2024 tarihleri arasında Ga-68 DOTATATE PET/BT görüntülemesi yapılmış 57 nöroendokrin tümör tanılı hasta retrospektif değerlendirildi. Hastaların yaş, histopatoloji, primer tümör lokalizasyonları, tümör boyutları, Ki-67 proliferasyon indeksleri, histolojik dereceleri ve tümör SUVmax değerleri kayıt edildi. Histolojik derece 2 ve 3 grup bir arada gruplandı (derece 2&3).

Bulgular: Yaş ortalaması 49,44 ± 17,20 idi. En sık biyopsi lokasyonları karaciğer (%28,07), mide (%21,05) ve pankreas (%19,30) idi. Ortalama Ki-67 proliferasyon indeksi 5 idi (çeyrekler açıklığı: 2 - 8). 19 hastada (% 33,33) derece 1, 35 hastada derece 2 (% 61,40) ve 3 hastada derece 3 tümör (%5,26) vardı. Tümörlerin SUVmax değerleri, tümör boyutları ve Ki-67 proliferasyon indeksleri ile, Ki-67 proliferasyon indeksleri de tümör boyutları ve mitoz sayıları ile pozitif korele idi. Derece 2&3 tümörlü hastalar daha ileri yaşlı olup tümör SUVmax değerleri derece 1 tümörlere göre anlamlı olarak daha yüksekti. ROC analizinde SUVmax değeri >12,5 eşiğinin derece 2&3 hasta grubunu %57,89 duyarlılık, %78,95 özgüllük, % 64,91doğruluk, % 84,62 pozitif öngörü değeri ve % 48,39 negatif öngörü değeri ile ayırt edebildiği gösterildi (EAA: 0,669, 95% CI: 0,526-0,811, *p=0,039*).

Sonuç: Nöroendokrin tümörlerde inisyal Ga-68 DOTATATE PET/BT'de primer tümöre ait SUVmax değerinin Ki-67 proliferasyon indeksleri ile pozitif korele olduğu ve 12,5 g/ml eşik değerinin üzerinde olmasının derece 2&3 hastaları erken dönemde yüksek pozitif öngörü değeri ile ayırt edebildiği gösterildi.

Anahtar Sözcükler: DOTATATE, Ga-68, NET, SUVmax, PET.

Introduction

Neuroendocrine tumors (NETs) are rare malignant neoplasms originating from neuroendocrine cells in various organs, which often express somatostatin receptors (SSTRs) on their surfaces (1). Their primary origin is the gastrointestinal tract (two-thirds) and pancreas, with 25% emerging from the bronchopulmonary tract, and rarely from other locations (2).

NETs are diagnosed pathologically and are classified into histological grades based on mitotic counts and Ki-67 proliferation index (PI). According to the 5th edition of the World Health Organization classification and grading criteria for digestive and thoracic NETs, patients are classified as low grade (grade 1), intermediate grade (grade 2), and high grade (grade 3) (3). For digestive NETs, patients with <2 mitoses/2 mm^2 or a Ki-67 PI of <3% are classified as grade 1, those with 2–20 mitoses/2 mm^2 or Ki-67 PI 3–20% as grade 2, and those with >20 mitoses/2 mm^2 or Ki-67 PI >20% as grade 3 (3). For thoracic NETs, patients with <2 mitoses/2 mm^2 are classified as grade 1; those with 2–10 mitoses/2 mm^2 as grade 2; and those with >10 mitoses/2 mm^2 and/or Ki-67 PI >30% as grade 3 (4,5).

It is well-established that NETs exhibit varying degrees of invasive biological behavior based on histological grade, which makes accurate grading and Ki-67 PI measurement critical for prognostication and management (6). These features are typically determined through post-surgical histopathological examination or invasive biopsy, and therefore, non-invasive methods that can aid in the early prediction of these characteristics can be highly beneficial.
Approximately 90% of NETs overexpress SSTRs on the cell membrane, making these receptors a key target for NET imaging and therapy (7). Positron emission tomography / computed tomography (PET/CT) with Gallium-68 (Ga-68)-labeled somatostatin analogs enables visualization of NETs by binding to SSTR subtypes 2 and 5 (8). Approved for use by the Food and Drug Administration in 2016, Ga-68 DOTATATE specifically binds to overexpressed SSTRs and is widely used in the initial staging of NETs, localization of primary tumors, preoperative staging, and patient selection for peptide receptor radionuclide therapy (9).

The most commonly used semi-quantitative parameter in PET imaging is the maximum standardized uptake value (SUVmax), which provides a numerical value allowing the assessment of tumoral radiopharmaceutical retention and tumor-to-background activity ratio, alongside qualitative visual data (10).

Our aim was to investigate whether the primary-lesion SUVmax value obtained from Ga-68 DOTATATE PET/CT could predict the histological grade and/or the Ki-67 PI of treatment naive NETs.

Material and Method

Patient Selection and Preparation

Patients who underwent Ga-68 DOTATATE PET/CT imaging in our nuclear medicine unit between January 2021 and April 2024 with a diagnosis of NET were retrospectively evaluated. Inclusion criteria were having a histopathological diagnosis of NET, a time interval of less than 1 month between biopsy and Ga-68 DOTATATE PET/CT imaging, not having received prior treatment or surgery, and absence of additional malignancy diagnoses. Patients were excluded if they lacked a definitive histopathological diagnosis, had a biopsy-to-imaging interval greater than 1 month, had undergone surgery or received treatment, or had concurrent malignancies.
This study was approved by the Ethics Committee of Başakşehir Çam ve Sakura City Hospital (Date: July 2024; Approval number: E-96317027-514.10-248465455). All diagnostic and therapeutic procedures were conducted in compliance with local national guidelines and the principles of the Declaration of Helsinki (1964) and its later amendments.

Ga-68 DOTATATE PET/CT imaging Image Acquisition

Prior to PET/CT imaging, patients were informed about the procedure both orally and in written form. The Ga-68 DOTATATE injection was performed (120-200 MBq) (80µg peptide per 14 mci), followed by a resting period of around 45-60 minutes. The patients were directed to assume a supine position for the imaging process and acquisition was performed from the vertex to the mid-thigh (Philips Ingenuity TF 64 PET/CT; Philips Medical Systems, OH, USA). Non-contrast CT obtained with low dosage exposure was used for attenuation correction, with 4-mm slice thickness and employing 113 mAS and 120 kV

settings. After completion of the CT, a 4-minutes-per-bed PET image acquisition was carried out. Reconstruction of images was performed with an iterative method that generated cross-sectional images on coronal and sagittal planes, as well as 3-dimensional projections.

Image Analysis

Ga-68 DOTATATE PET/CT images were analyzed by two experienced nuclear medicine specialists. In cases of disagreement, a consensus was reached through detailed discussion. SUVmax values were recorded by drawing a volume of interest around the primary lesion.

Table I. Summary of variables

Age	49.44 ± 17.20
Sex	
Male	25 (43.86%)
Female	32 (56.14%)
Location	
Lung	5 (8.77%)
Gastric	12 (21.05%)
Pancreas	11 (19.30%)
Liver	16 (28.07%)
Small bowel	4 (7.02%)
Colon	5 (8.77%)
Rectum	4 (7.02%)
SUVmax	10.5 (4.9 - 31.0)
Tumor size (cm)	3.0 (1.7 - 5.9)
Ki-67 (%)	5 (2 - 8)
Grade	
Grade 1	19 (33.33%)
Grade 2	35 (61.40%)
Grade 3	3 (5.26%)
Mitosis	1 (0 - 3)
Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables.	

Pathology

Histopathological diagnoses, Ki-67 PI, and mitotic counts were assessed using pathology slides. For Ki-67 PI, immunohistochemical staining was applied to the slides and 500–2000 neoplastic cells were evaluated at 400X magnification. Cells showing nuclear staining in the hotspot areas (regions with the most intense staining) were considered regardless of staining intensity. The percentage ratio of tumor cells stained with Ki-67 to the total tumor cells in the selected area was defined as Ki-67 PI (11).

Table II. Correlations between variables

		Tumor size (cm)	Ki-67 (%)	Mitosis
SUVmax	*r*	*0.326*	*0.368*	*0.107*
	p	***0.013***	***0.005***	*0.426*
Tumor size (cm)	r		*0.407*	*0.126*
	p		***0.002***	*0.348*
Ki-67 (%)	r			*0.488*
	p			***<0.001***
r: Spearman correlation coefficient				

Mitotic counts were assessed on H&E (Hematoxylin-Eosin) stained slides and slides stained immunohistochemically with PHH3. Counts were performed over at least 10 mm^2, and the number of mitoses per 2 mm^2 was recorded as standard in tumor regions with the highest mitotic activity (corresponding to 10 high-power fields at 400X magnification).

Table III. Summary of variables with regard to grade

	Grade			
	Grade 1 (n=19)	Grade 2&3 (n=38)	Test statistic	*p*
Age	41.79 ± 18.10	53.26 ± 15.60	Student's t test, t=-2.481	***0.016***
Sex				
Male	9 (47.37%)	16 (42.11%)	Chi-square test, X^2=0.009	*0.925*
Female	10 (52.63%)	22 (57.89%)		
Location				
Lung	1 (5.26%)	4 (10.53%)	Fisher-Freeman-Halton test, Exact=2.566	*0.908*
Gastric	6 (31.58%)	6 (15.79%)		
Pancreas	3 (15.79%)	8 (21.05%)		
Liver	5 (26.32%)	11 (28.95%)		
Small bowel	1 (5.26%)	3 (7.89%)		
Colon	2 (10.53%)	3 (7.89%)		
Rectum	1 (5.26%)	3 (7.89%)		
SUVmax	6.1 (4.2 - 12.3)	16.55 (5.9 - 38.2)	MWU test, U=239.0	***0.039***
Tumor size (cm)	2.5 (1.0 - 5.0)	3.75 (1.7 - 6.0)	MWU test, U=288.0	0.216
Ki-67 (%)	1.5 (1 - 2)	7 (5 - 10)	MWU test, U=000.0	***<0.001***
Mitosis	1 (0 - 1)	1 (1 - 5)	MWU test, U=200.5	***0.005***
Descriptive statistics are presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile - 75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables. MWU: Mann Whitney U. Statistically significant p values are shown in bold.				

Table IV. Performance of SUVmax to predict grade 2&3 tumors, ROC curve analysis

Cut-off	>12.5
Sensitivity	57.89%
Specificity	78.95%
Accuracy	64.91%
PPV	84.62%
NPV	48.39%
AUC (95% CI)	0.669 (0.526 - 0.811)
p	0.039

ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence interval

In cases of discordance between mitotic count and Ki-67 PI, the higher value was preferred (12). Grade 2 and grade 3 tumors were combined into a single group designated as the 'grade 2&3' group due to the presence of only three patients with grade 3 tumor –since it would have been inappropriate to perform statistical analysis for a group with only three samples.

Table V. Association between variables and grade 2&3 tumors, multivariable logistic regression analysis

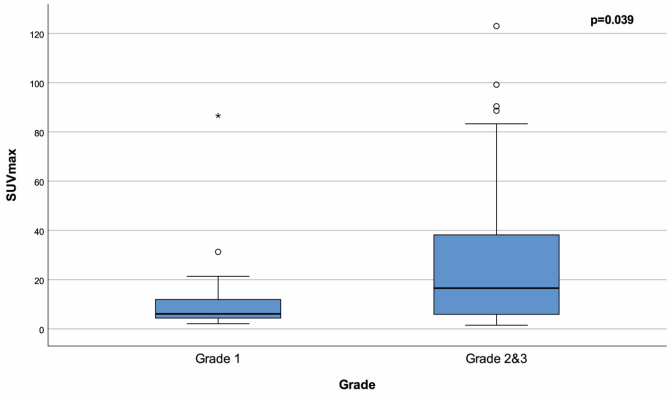
	β coefficient	Standard error	*p*	Exp(β)	95% CI for Exp(β)	
Age	0.055	0.023	***0.017***	1.056	1.010	1.104
SUVmax, >12.5	1.895	0.769	***0.014***	6.654	1.473	30.051
Mitosis	0.388	0.191	***0.042***	1.474	1.014	2.143
Constant	-3.340	1.290	*0.010*	0.035		

Nagelkerke R^2=0.433, CI: Confidence interval, Statistically significant p values are shown in bold.

Statistical Analysis

A p-value of less than 0.05 was deemed indicative of statistical significance, and all tests were two-tailed. Data analyses were conducted using SPSS version 25.0 (IBM, Armonk, NY, USA). Continuous variables were assessed for normality using histograms and Q-Q plots. Descriptive data were expressed as mean ± standard deviation for normally distributed variables, median (interquartile range) for those not normally distributed, and frequency (percentage) for categorical data. The Student's t-test was used to compare age, which was a normally distributed continuous variable. The Mann-Whitney U test was used for the comparisons of SUVmax, tumor size, Ki-67 and mitosis, which were non-normally distributed continuous variables. Sex (categorical variable) was analyzed with the chi-square test and location (categorical variable) was analyzed with the Fisher-Freeman-Halton test due to the fact that some cells in the confusion matrix had expected counts less than five. Correlations between continuous variables (SUVmax, tumor size, Ki-67 and mitosis) were examined using Spearman's correlation coefficient due to non-normal distribution. Significant factors associated with grade 2&3 tumors were identified through multivariable logistic regression analysis. The initial model included variables found to be statistically significant in univariable analyses.

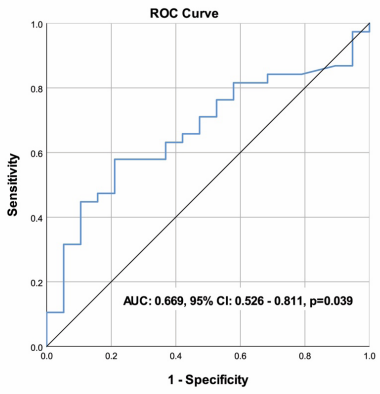
Figure I. Box-plot of the SUVmax with regard to grade



Results

We included 57 patients with NET (25 males and 32 females) into the study, mean age was 49.44 ± 17.20. The most common biopsy locations were the liver (28.07%), stomach (gastric; 21.05%) and pancreas (19.30%). Nineteen (33.33%) patients were grade 1, thirty-five (61.40%) patients were grade 2, and three (5.26%) patients were grade 3. Median Ki-67 PI was 5 (interquartile range 2 - 8) (Table I).

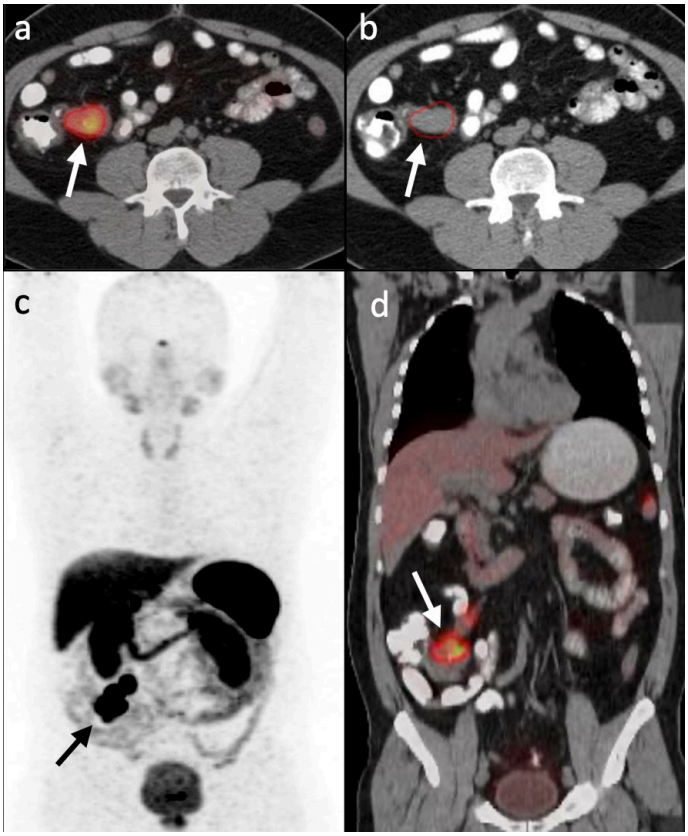
Figure II. ROC curve of the SUVmax value in the prediction of grade 2&3 tumors



Relationship Between SUVmax and Ki-67

SUVmax was positively correlated with tumor size (Spearman correlation coefficient, *r=0.326, p=0.013*) and Ki-67 (Spearman correlation coefficient, *r=0.368, p=0.005*). Ki-67 was positively correlated with the tumor size (Spearman correlation coefficient, *r=0.407, p=0.002*) and it was also correlated with mitosis as anticipated (Spearman correlation coefficient, *r=0.488, p<0.001*). There were no significant relationships between SUVmax and mitosis, and between tumor size and mitosis (Table II).

Figure III. Baseline 68Ga-DOTATATE PET/CT images of a patient with grade 2&3 neuroendocrine tumor in the small intestine with a maximum standard uptake (SUVmax) value of 31.5 g/ml (greater than the >12.5 g/ml threshold). Primary tumor (arrow) on axial fused image (a), axial CT images (b), maximum intensity projection (MIP) image (c) and coronal fused image (d).



Relationship Between SUVmax and Grade

Age (Student's t test, *t=-2.481, p=0.016*), SUVmax (Mann Whitney U test, *U=239.0, p=0.039*) and mitosis (Mann Whitney U test, *U=200.5, p=0.005*) values were significantly higher in grade 2&3 tumors than in grade 1 tumors (Figure I). We found no significant differences between grade 1 and grade 2&3 tumors in terms of sex, location, and tumor size (Table III).

SUVmax had significance in discriminating between grade 1 and grade 2&3 tumors with an area under ROC curve of 0.669 (95% CI: 0.526 - 0.811, *p=0.039*) (Figure II). With an optimal cut-off value of 12.5 (higher values predict grade 2&3 tumors), SUVmax had an overall accuracy of 64.91%, with 57.89% sensitivity, 78.95% specificity, 84.62% positive predictive value, and 48.39% negative predictive value (Table IV). Logistic regression with a multivariable model adjusted by age (*p=0.017*) showed that grade 2&3 tumors were independently associated with having a high SUVmax (>12.5) (OR: 6.654, 95% CI: 1.473 - 30.051, *p=0.014*) and high mitosis value (OR: 1.474, 95% CI: 1.014 - 2.143, *p=0.042*) (Table V). A representative imaging result is provided in Figure III.

Discussion

In NETs, early and accurate determination of prognostic features such as histological grade and Ki-67 PI is crucial for surgical planning, which is one of the most important treatment steps, as well as other management decisions, the application of correct treatments, and to predict prognosis (13,14). In this study, we concluded that there is a positive correlation between primary lesion SUVmax value and tumor size, and Ki-67 PI in early staging Ga-68 DOTATATE PET/CT imaging in NETs. In fact, SUVmax values of >12.5 appear to predict grade 2&3 tumors with a high positive predictive value (84.62%). Although the sensitivity and specificity are not very high, we think that these findings may have clinical relevance for the purpose of distinguishing grade 2&3 NETs with non-invasive imaging in the preoperative period – particularly considering the paucity of evidence on this subject.

Prior studies evaluating the relationship between the SUVmax value (obtained from Ga-68 labeled somatostatin analogues PET/CT) and histopathological findings in NETs evaluate the results based on pathological findings of the lesion with the highest SUVmax value and any biopsied lesion. Unlike our study, this approach carries the risk of ignoring the heterogeneous distribution of the disease (15,16). It has been shown that the lesion with the highest SUVmax value may be pathologically dissimilar to the biopsied lesion. Furthermore, the heterogeneity

of primary and metastatic lesions may be different, and it is also possible that even metastatic lesions located in the same organ (liver) in the same patient may have different histologic grades (17). Chan et al., in their study of lesion SUVmax values obtained from Ga-68 DOTATOC imaging and the pathology results of the same NET lesions, reported an inverse correlation between Ki-67 PI and SUVmax. They stated that this may be due to the lack of correlation between tumor size and SSTRs uptake in their patient population (18). Although the methodology was similar to ours, we report positive correlations between lesion SUVmax, tumor size and Ki-67 PI values, and we believe that the difference may be attributed to patient characteristics and the types of compounds used during imaging. Nonetheless, these results necessitate the investigation of how the SUVmax-tumor size relationship might be associated with the correlations between SUVmax and Ki-67.

Although NETs generally show high SSTRs expression similar to the neuroendocrine cells from which they originate (since they are well-differentiated tumors), it is also known that SSTR expression declines in poorly differentiated tumors (19). Similarly, a decrease in Ga-68 DOTATATE uptake and lower SUVmax values are expected in poorly-differentiated neuroendocrine carcinomas with Ki-67 PI values of >55% due to loss of SSTR expression (9). In a study in which the majority of the patient population (84.6%) consisted of patients with strongly-positive Ki-67 PI values, a negative correlation was reported between Ki-67 PI and Ga-68 DOTATATE SUVmax values (20). There are other studies in the literature reporting that SUVmax value is lower in higher grade patients with high Ki-67 PI compared to those with low grade tumors (16,21). The reason for the positive correlation between Ki-67 PI and SUVmax in our patient population might be associated with the generally low Ki-67 PI values detected in the cohort –with a 75% percentile value of 8%. This again demonstrates the heterogeneity of the disease and warrants further studies with larger patient groups.

Tumor histological grade can traditionally be determined by percutaneous core biopsies or surgical excision from the most easily and safely accessible region of the lesion (19). There may be differences in histopathological findings depending on the site of biopsy, which can be explained by tumor heterogeneity, and therefore it is possible to obtain different histologic grades from biopsy material acquired from different regions of the lesion (19). In our study, a SUVmax value of >12.5 g/ml obtained from the tumor was found to be relatively capable in predicting grade 2&3 lesions with a high positive predictive value. This supports the literature on this topic by revealing that molecular imaging with Ga-68 DOTATATE PET/CT can benefit the characterization of lesions that are observed throughout the body (22,23). Being able to differentiate grade 2&3 and grade 1 lesions non-invasively in the early period may facilitate better planning of personalized treatments (13), which could improve outcomes.

The limitations of the study are that it was single centered, retrospective in design, consisted of a small number of patients, and there were considerably fewer grade 3 patients compared to other groups (5.26%). Another limitation is that other volumetric parameters that can be obtained from these lesions (such as MTV and TLG) were not examined in the Ga-68 DOTATATE PET/CT imaging of individuals.

Conclusion

Our study demonstrated that a SUVmax threshold value of >12.5 g/ml obtained non-invasively from the initial Ga-68 DOTATATE PET/CT study of the primary lesion in patients with NETs can distinguish grade 2&3 patients from grade 1 patients with a high positive predictive value and a respectable specificity. We also found that SUVmax value was positively correlated with Ki-67 PI, another important prognostic marker of the disease.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Effects of Trauma on the Retina and Lens

Travmanın Retina ve Lens Üzerine Etkileri

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Derleme | Review
Doi: https://doi.org/10.52827/hititmedj.1551949
Geliş Tarihi | Received: 17.09.2024
Kabul Tarihi | Accepted: 16.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Çağlar Ç. Effects of Trauma on the Retina and Lens. Hitit Medical Journal 2025;7(1):109-117. https://doi.org/10.52827/hititmedj. 1551949

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Makale Derleme türünde olduğundan etik kurul onayına gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez ÇÇ Tasarım ÇÇ Veri Toplama/Veri İşleme ÇÇ Veri Analizi ÇÇ Makalenin Hazırlanması ÇÇ.
Hasta Onamı: Makale Derleme türünde olduğundan hasta onamına gerek yoktur..
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Ethical committee approval is not required.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: ÇÇ Design: ÇÇ Data Collection/Data Processing: ÇÇ Data Analysis: ÇÇ Manuscript Preparation: ÇÇ.
Informed Consent: Our University Clinical Research Ethics Committee has confirmed that no consent for publication from patients is required.
Financial Disclosure: There are no financial funds for this article.

Effects of Trauma on the Retina and Lens

ABSTRACT
Ocular trauma is very common in our country. Especially, young and active people are affected by such traumas. Loss of vision in ocular trauma is most commonly caused by lens and retina trauma. The aim of this review is to provide an overview of traumatic lens and retina injuries and to discuss current treatment methods for traumatic cataract and traumatic retinopathy.

Keywords: Cataract, retinopathy, trauma.

ÖZET
Oküler travma ülkemizde çok sık görülmektedir. Özellikle genç ve aktif insanlar bu tür travmalardan etkilenmektedir. Oküler travmada görme azlığına en sık lens ve retina travması neden olur. Bu derlemede amaç travmatik lens ve retina yaralanmalarına genel bir bakışla birlikte travmatik katarakt ve travmatik retinopatinin güncel tedavi yöntemlerini tartışmaktır.

Anahtar Sözcükler: Katarakt, retinopati, travma.

Giriş

Travmaya bağlı göz yaralanmaları, önlenebilir görme azlığı ve körlüklerin en sık sebeplerinden biridir (1). Tüm vücut yaralanmalarının yaklaşık %7'si, göz hastalıklarının %10 kadarını göze ait travmalar oluşturmaktadır (2). Direkt göz travması insidansı 3/100.000 olduğu tahmin edilmektedir (3). Göz travmaları, genç ve üretken yaş grubunda ve erkeklerde daha sık görülmektedir. Amerika Birleşik Devletleri'nde erkeklerde yaygınlık %13,5'tur (4). Göz travmalarının gerek travma anında gerekse de sonraki dönemde oluşturduğu görme problemleri ve sosyoekonomik yönleri nedeniyle hastaya ve topluma olan etkileri önemlidir (5).

Topluma ve hastaya fonksiyonel, medikal ve sosyoekonomik yönden büyük yük getiren, bir genel sağlık problemi olan göz travmaları önlenebilir nitelikte olması nedeniyle önemlidir. Gerek künt, gerekse de perforan yaralanmanın gözde en sık etkilediği dokulardan ikisi lens ve retina olup, travmanın bu iki dokuda yol açtığı yaralanmayı acil dönem ve sonrasında uygun bir şekilde yaklaşmak ve tedavi etmek görme azlığının ve körlüğün önlenmesinde son derece önemlidir. Özellikle son yıllarda bu iki yapının tedavisinde gelişen yenilikler nedeniyle bu derlemede travmaya bağlı oluşan lens ve retina hasarı ve güncel tedavi yaklaşımlarından bahsedilecektir.

Travmatik katarakt ve travmaya bağlı lens yaralanmaları

Lens hasarı, künt, penetran, elektirik/yıldırım çarpması, termal ve radyasyona bağlı travma sonucu oluşabilir (6). Künt travmada göz ön arka çapı aniden kısalır, ekvatorda genişleme ve gerilme oluşur. Künt travmayla birlikte lens içine sıvı girişi ve lens fibrillerinde şişme sonucu lens ön kapsülü altında opaklaşma ve genelde travmaya özgü çiçek şekilli (rozet) katarakt veya noktasal opasiteler gelişir. Dairesel şekilli anterior subkapsüler opasite olan Vossius halkası oluşabilir. Zamanla birlikte arka subkapsüler katarakt gelişebilir. Künt travmanın lense yaptığı darbe etkisiyle lensi asıcı zonüllerde hasara yol açarak lens subluksasyonu ve dislokasyon meydana gelebilir. Subluksasyon sağlam kalan zonüller tarafına doğru olur. Göz hareketiyle iridodenezis ve fakodenezis izlenebilir. Sublukse lensin kenarı midriyazis sonucu görülebilir. Tek gözde diplopi, astigmat ve diğer refraksiyon kusurları oluşabilir (7). Zonüler ayrılmanın olduğu kısımda lensin arkaya doğru rotasyonuyla derin ön kamara ve vitreus inkarserasyonunun görülmesi zonül hasarının işaretidir (8). Dislokasyon tüm zonüllerin rüptürü sonucu lensin ön kamaraya ya da vitreus boşluğuna doğru yer değiştirmesidir.

Penetran travmada, travma sebebi cisim lense kadar ulaşırsa ön kapsülde rüptür oluşur. Eğer lens ön kapsülündeki rüptüre bağlı açıklık küçük ise lens içine hızlı sıvı girişi lokalize bir lens opasitesine yol açarken, daha büyük bir açıklık, tüm lensin hızlıca opaklaşmasına neden olur. Rüptür olan ön kapsülden çıkan lens proteinleri ön kamaraya geçerek trabekülumu tıkar ve travmanın etkisiyle oluşacak trabeküler ağ ödemi ile birlikte göz içi basıncı (GİB) artışı ve enflamasyon oluşur. Bu durum fakojenik üveit ve fakolitik glokom adı verilen durumlara yol açabilir. Fakoanaflaktik endoftalmi ismi ile de anılmaktadır. Kapsüler hasarın ardından günler haftalar sonra ortaya çıkan gözde kızarıklık, ağrı, fotofobi yapan bir travmatik ön üveittir. Farklı şiddetteki granülomatöz ön üveit, korneada iri koyun yağı keratik presipitatlar, hipopiyon olabilir. GİB yükselebilir ve akut glokom krizine yol açabilir (9). Tedavide yoğun topikal steroidler ile birlikte sikloplejik ve GİB düşürücü ajanlar kullanılır. Ön kamarada lens bakiyesi varsa, enflamasyon şiddeti artacağından ameliyatla temizlenmelidir (10).

Elektrik çarpması veya yıldırım travmasına bağlı kataraktlarda ise protein koagülasyonu ile oluşan ozmotik değişiklikler ön veya arka subkapsüler bölgede eğreltiotu görünümlü gri beyaz opasiteler meydana getirir. X ışını gibi iyonize radyasyon, kapsül epitel hücre DNA'sını bozarak, protein ve enzim transkripsiyonu ve hücre bölünmesini etkiler. Arka polar katarakt gelişimine neden olur. Kızılötesi gibi iyonize olmayan radyasyon, özellikle cam üfleyicisi ve koruyucu gözlük kullanmadan fırın karşısında çalışan işçilerde katarakt gelişimine neden olur. İriste lokalize bir ısı artışı ön kapsülde eksfoliyasyon ve arka subkapsüler katarakta neden olur (11).

Travmatik kataraktta güncel tedavi

Travma sonrası kataraktta tedavi cerrahidir. Kataraktın ortaya çıkma hızı, kapsülün bütünlüğü, ilgili epitel hücrelerinin sayısı ve inflamatuar yanıtın derecesi ile ilişkilidir (12). Bazı durumlarda travmatik katarakt yıllarca takip edilebilirken, bazı durumlarda ise operasyon için acele edilmelidir. Travmatik kataraktlarda cerrahi endikasyonları ciddi görme

azlığı, lense bağlı glokom, kapsül yırtılması ve lens şişmesi, posterior patolojilerin görülmesini engelleyen lens opasiteleridir. Perforan yaralanmalarda lens cerrahisinin aynı seansta veya daha sonra yapılması konusu tartışmalıdır. Penetran yaralanma sonucu ön kapsül rüptürü varsa ve ön kamarada lens materyali varsa bu lens materyali acilen temizlenmeli ve bunun için cerrahi birkaç gün içinde mümkün olan en kısa zamanda yapılmalıdır. Aynı seansta hem penetran korneal yaralanma tamiri, hem de lens cerrahisi yapılması daha uygun bir seçenektir. Aynı seansta yapılmasının avantajları tek seferde bütün cerrahinin tamamlanması, lense bağlı enflamasyonun kontrolü, GİB yüksekliğinin önlenmesi, görme rehabilitasyonunun erken sağlanabilmesidir. Cerrahide görme aksının temizlenmesi arka segmentin ve optik diskin direkt olarak görüntülenmesine ve varsa bu segmentteki patolojilerinde tedavisine olanak sağlar. Dezavantajları ise yanlışlıkla şeffaf lensin alınması, ön kamarada aşırı fibrinoid reaksiyon, pupiller siklitik membran oluşumu, hifema, kornea ödemi gibi komplikasyonların sık görülmesidir. Ayrıca intraoküler lens (İOL) gücü hesabının zorluğu, İOL üzerine enflamatuar debris çökmesi, enfeksiyon riskinin artması gibi zorlukları da beraberinde getirebilir (13). Lens periferinde, küçük, sınırlı kapsül yırtıkları, kapsül altı küçük yabancı cisimler için cerrahi tedavide acele edilmemelidir çünkü bu tür gelişen katarakt lokalize kalmaya eğilimlidir. Eğer penetran travma sonucu lens hasarı çok fazla değilse, kornea tamir edilirken lens cerrahisi ikinci seansa bırakılabilir. İkinci seansta lens cerrahisinin avantajları daha az enflamasyon, planlı bir cerrahi metod ve sürprizlere daha az açık olması, İOL implantasyon zamanının tespiti, daha doğru İOL gücü hesaplanması yapılabilmesidir (14-15). Primer veya ikinci seansta katarakt cerrahisi kararında hasta yaşı, lensin durumu, patolojiye vitreusun eşlik edip etmediği, cerrahın tecrübesi, ameliyathanenin şartları ve ekipmana göre karar verilir (16). Küçük çocuklarda görme ekseninin kapalı olması kısa sürede bile ambliyopiye neden olabileceğinden aynı seansta cerrahi ya da erken sekonder cerrahi açısından değerlendirilmelidir (17-18). Eğer böyle bir durum yoksa lens temizliği yapıldıktan sonra enflamasyonun azalması için birkaç hafta beklenebilir ve sonrasında İOL implantasyon cerrahisi planlanabilir. Travmatik katarakt sonucu ambliyopi gelişme riski %6-51 arasında bildirilmiştir (19). Ön segment travmalı gözlerin %42,9'unda ultrason biyomikroskopide gizli zonüler hasar mevcuttur. Bu durum, cerrahi sırasında vitreus prolapsusu ve lensin vitreusa düşmesi riskinin daha yüksek olmasına neden olabilir. Bundan dolayı bu gözlerde travmatik katarakt cerrahisi öncesi ultrason biyomikroskopi yapılması faydalıdır (20).

Penetran yaralanma nedeniyle lens ön kapsülü rüptüre olmuşsa, ön kapsül devamlı ve kurvilineer bir kapsüloreksis haline getirilmelidir. Ön kapsülün düzensiz halde olması, implante edilecek intraoküler lensin dislokasyonuna neden olabilir. Ön kamarada lens materyali ile birlikte vitreus da olabilir. Eğer sadece ön kapsül hasarlı ise travmatik katarakt cerrahisi yeterli olurken, arka kapsül açıklığı ve vitreus inkarserasyonu mevcut ise pars plana lensektomi-vitrektomi tercih edilmelidir. Bu durumda ön kamaraya triamsinolon da verilerek, ön vitrektomi ile ön kamaradaki vitreus ve lens materyali temizlenmelidir. Aynı seansta İOL yerleştirilebilir ya da sonraki seansa bırakılabilir. Eşlik eden bir arka segment patolojisi varsa bu durumda pars plana lensektomi vitrektomi yaklaşımı daha uygun olacaktır. Pars plana lensektomi yapılan arka kapsülü açık olgulara eğer ön kapsül desteği yeterli ise, sulkusa aynı seansta veya sonraki bir seansta sekonder İOL implantasyonu yapılabilir (21-22). Kapsül desteği olmayan olgularda skleral fiksasyon teknikleri kullanılabilir. Travmatik kataraktlı hastalar daha genç yaş grubunda olduğu için bu olgularda en emniyetli ve uzun süre skleraya İOL stabilizasyonu sağlayan teknikler tercih edilmelidir (23). Bu olgularda hangi tekniğin kullanılması gerektiği ile ilgili literatürde bir araştırma yoktur.

Göz içi lensini de içeren yapay iris implantları, travmaya bağlı kataraktlarla birlikte olan geniş travmatik iris defektlerinin tedavisi için etkili bir seçenektir ve kozmetik açıdan tatmin edici ve iyi fonksiyonel sonuçların yanı sıra yüksek hasta memnuniyetini sağlar. Ancak tecrübeli ellerde yapılması gerekmesi ve glokom gibi ortaya çıkabilecek çeşitli ciddi komplikasyonlar nedeniyle dikkatle yapılması ve takip edilmesi gereken bir cerrahidir (24-25).

Travmatik Retinopati

Oküler travma direkt ya da indirekt, penetran ya da künt olabilir. Travmanın tipine göre oluşan şok dalgasının şiddetine göre çeşitli retinal patolojiler

oluşabilir.

Kommosyo Retina (Berlin ödemi); Künt oküler travma sonucu retinanın derin dokularının beyazlaşması ile karakterize bir durumdur. Santral veya periferik retinada oluşabilir ama sıklıkla temporal retinadadır. Retina beyazlaşması ile birlikte retinal ve subretinal hemorajilerle karakterize bir tablodur. Prognoz iyidir ve genelde 6 hafta içinde iz bırakmadan iyileşir. Şiddetli olgularda ilerleyici pigmenter dejenerasyon ve maküler hol formasyonu gelişebilir. OCT'de fotoreseptör dış segment ve iç/dış segment birleşim bölgesinde hiporeflektivitenin yanısıra kötü prognoz göstergesi olan dış limitan membranda bozulmalarla karakterize morfolojik değişiklikler gösterilmiştir (26). Ayrıca subfoveal koroidal kalınlıkta artış gösterilmiştir (27). Bir başka çalışmada ise düzensiz elipsoid zon ve fokal hiporeflektif elipsoid zon mikrolevasyonu şeklinde iki adet yeni OCT bulgusu tarif edilmiştir (28). Eğer travma şiddetli ve makula tutulumu ağırsa görme prognozu kötüdür. Bilinen bir tedavisi yoktur ama fotoreseptör iyileşmesi 1 hafta içinde başlar. Genel olarak iyi bir prognozu vardır ve vakaların çoğu, hiçbir sekel olmaksızın 4 hafta içinde tamamen düzelir. Bununla birlikte, daha ciddi vakalarda hastalarda görme bozukluğu ve parasantral skotomlarla sonuçlanan kalıcı maküla hasarı oluşabilir. Bazı vakalarda intraoküler ve sistemik steroidin yararı gösterilmiştir (29-30).

Koroid rüptürleri; Koroid, Bruch membranı ve retina pigment epitelini kapsar. Beyaz-sarı eğrisel veya hilal şeklinde lezyonlar olarak ortaya çıkar ve sonuçta retinal skarlaşmaya yol açar. Direkt göz yaralanmalarında bu yırtıklar ora serratanın anteriorunda ve paralelinde yerleşirken, indirekt yaralanmalarda optik diskle eş merkezli yırtıklar oluşur. Tek veya çoklu olabilir. Spontan regresyon gösterebilir, Makulayı tutarsa prognoz kötüdür ve görme keskinliği düşer. Geç dönemde rüptür zemininde subretinal neovasküler membran gelişebilir (31-33). Koroid rüptürünün bir tedavisi yoktur. Ama rüptür zemininde gelişen koroid neaovasküler rmembran için (vakaların %5-12'sinde görülür) antiVEGF tedavisi etkilidir. Rüptür zemininde gelişen membranlar genelde iyi prognozludur ve tedaviyle tamamen iyileşebilirler. Yaşa bağlı makula dejenerasyonuna göre daha az enjeksiyon gerekir. Genelde ilk 1 yılda gelişselerde, 30 yıla kadar neovasküler membran gelişen olgular gösterilmiştir (31,34).

Purtscher's retinopatisi (travmatik retinal anjiyopati); Optik sinir başı ve fovea çevresinde paravasküler alanın tutulmadığı intraretinal hemorajiler ve retinada fazla sayıda 'pamuk yünü lekeleri' olarak adlandırılan Purtscher lekeleri (retina arteriolleri ve venülleri arasında poligonal retinal beyazlık) ile karakterize oklüzif bir mikrovaskülopatidir (35). Purtscher retinopatisi olan hastalar genellikle travmadan iki gün sonra her iki gözde ani başlangıçlı ağrısız görme azalmasıyla başvururlar. Ciddi göğüs kompresyonu, kafa travması, uzun kemik kırılmaları, barotravma ve bebeklerde şiddet görme gibi durumlardan sonra da görülebilir (36). Bu durumlar gibi Purtscher retinopatisi gibi özellikler açık travma öyküsü olmadan ortaya çıktığında buna Purtscher benzeri retinopati denir. OCT'de Orta ve derin retinal kılcal pleksusun iskemisine bağlı olarak iç nükleer tabakanın hiperreflektivitesi ile karakterize olan parasantral akut orta makulopati (PAMM), akut fazda bir özellik olabilir. Geç fazdaki özellikler arasında retina incelmesi ve fotoreseptör kaybı bulunur (37). Genel olarak bir tedavisi olmamakla birlikte bir çalışmada günde üç doz intravenöz metilprednizolon tedavisi (1000 mg) ve ardından oral steroidlerle devam etmenin görsel ve anatomik iyileşme sağladığı gösterilse de (38) faydasının olmadığını gösteren çalışmalarda mevcuttur (39-40). Maküla ödemi olan vakalar, bevacizumab gibi anti-vasküler endotelyal büyüme faktörü ajanlarından faydalanabilir (41). Trombotik mikroanjiyopati ve Purtscher benzeri retinopatisi olan bir vaka, ekulizumab (C5'in C5a ve C5b'ye ayrılmasını engelleyerek kompleman sistemin terminal yolunu bloke eden bir monoklonal antikor) ile başarılı bir şekilde tedavi edilmiştir (37). Retinopati için denenen diğer tedaviler arasında oral nonsteroid anti-inflamatuar ilaçlar (indometasin) ve papaverin hidroklorür yer alır (42). Hiperbarik oksijende denenmiştir ama faydası gösterilememiştir (40). Birçok vakanın patogenezinde önemli bir faktör olan trombotik mikroanjiyopatiyi yönetmek için gelecekte araştırmalara ihtiyaç vardır. Bazı olgularda geç dönemde optik sinirde ve makulada atrofi ile sonuçlanıp ciddi görme kaybına sebep olabilir (43).

Travmatik retina dekolmanları (RD) önemli bir morbidite nedenidir. Yırtıklı RD'lerin %10'u travmaya bağlı gelişmektedir ve travmatik RD'lerin büyük kısmı künt yani kapalı göz travmalarına bağlıdır (44). Künt travma gözde şok dalgasına, negatif basınca ve

eylemsiz harekete yol açar (45). Özellikle travmadan etkilenen erkek ve gençlerde oluşur (46). RD'lerin travmadan hemen sonra gelişmesi gerekmez. Aylar hata yıllar sonra bile travmaya bağlı retina dekolmanları gelişebilir. 67 gözün dahil olduğu bir çalışmada travma ile RD arasındaki medyan ve ortalama aralık süreleri sırasıyla 23 ve 162 gündü. Vakaların %80,6'sı ve %89,6'sı sırasıyla 6 aydan ve 2 yıldan az latent aralık süresine sahipti (47). Travma sonrası gelişen at nalı yırtıklar veya kommasyo retinada gelişen retinal iskemi bölgelerinde iskemik atrofik delikler şeklinde retinal yırtıklarda görülebilmektedir. Ora serrata da vitreus bazının ayrılması ve arka yüzü boyunca traksiyonuyla retinal diyalizler gelişebilir. En sık superonazal ve inferotemporal kadranda gözlenir. Travmanın tarzına, hastanın yaşı ve fakik olup olmamasına, retinadaki yırtığın ve dekolmanın yeri ve durumuna göre hastalarda pars plana vitrektomi, skleral buckle ya da pnömotik retinopeksi tercih edilebilir ve her bir yöntemin başarısı %75'in üzerinde bulunmuştur. Ama vakaların çoğunda travmanın etkisine bağlı retinal hasar nedeniyle fonksiyonel başarı daha azdır (47). Özellikle PVR, total RD ya da alt yarı ve çoklu retina yırtıklarına bağlı gelişen RD'ler başarısızlık sebepleridir (48). Yine preoperatif az görme, eşlik eden vitreus hemorajisi ve lens yaralanmaları ve makulanın tutulduğu dekolmanlar görsel açıdan kötü prognostik faktörle ilişkilidir (49). Penetran ya da açık göz yaralanması sonucu travmatik traksiyonel retina dekolmanı oluşabilir. Skleraya penetran yaralanma sonucu yara yerinden vitreus inkarserasyonu gelişebilir. İlerleyen dönemlerde epiretinal fibrozisin yol açtığı kontraksiyon sonucu anterior traksiyonel retina dekolmanları oluşabilir (49). Bu tür traksiyonel RD gelişmemesi için tetikleyici travmadan sonraki yedi gün içinde erken müdahale, proliferatif vitreoretinopatiyi ve postoperatif endoftalmiyi azaltmada avantaj sağlarken, daha sonraki müdahale, özellikle eş zamanlı açık glob yaralanmaları vakalarında, inflamasyon ve kanama riskini azaltmada avantaj sağlar (50). Travmalı olgularda mutlaka retina muayene edilmeli ve oluşmuş retinal yırtık ve diyalizleri dekolman gelişmeden saptayıp proflaktik retinopeksi için laser fotokoagülasyon veya kriyo uygulamak gereklidir (51). Dolayısıyla bu hastaların erken teşhisi önemlidir. Şiddetli travmalardan sonra pupil yeterince dilate edilerek (dar pupilde retina periferinde oluşan yırtıklar gözden kaçabilir) tam bir retina muayenesi yapılmalı ve bu muayene birkaç hafta içinde tekrarlanmalıdır.

Travmatik maküla delikleri (TMD), anteroposterior ve tanjansiyel vitreoretinal traksiyondan kaynaklanır ve Berlin ödemi ve subretinal sıvı gibi eş zamanlı ek patolojiler gösterebilir (52). Watzke-Allen testi genellikle pozitiftir ve Amsler testinde merkezi metamorfopsi görülür (53). Aylar boyunca kademeli olarak gelişen idiyopatik deliklerin aksine TMD'ler genellikle travmadan hemen sonra oluşur (54). TMD'de kendiliğinden kapanma bildirildiği için bir süre takip edilmesi gerekir eğer delik kapanmazsa vitrektomi ile cerrahi kapatma yapılmalıdır. Miller ve arkadaşları TMD'lerin uzun vadeli takip serisinde çocuklarda %50 ve yetişkinlerde %28,6 kendiliğinden kapanma oranı tespit ettiler. Bu çalışmada TMD'ler ortalama 5.6 haftada kendiliğinden kapandı ve hiçbiri 67,3 hafta sonra müdahale edilmeden kapanmadı (55). Vitrektomi, PVD indüksiyonu ve ILM soyulması (TMD'yi örtmek için bir ILM flebi ile veya flepsiz) %100'e varan anatomik başarı oranlarıyla ilişkilidir (52,56).

Travmatik Optik Nöropati (TON), kraniomaksillofasiyal travma sonrasında orbitanın üstündeki frontal ve temporal bölgelerin dış kuvvetler tarafından travmatize edilmesi sonucu çevre dokuların yaptığı kompresyon, kırık kemik parçaları veya penetran travma nedeniyle direkt veya indirekt meydana gelir. Dar optik kanalda hareket eden intrakanaliküler segment en yüksek yaralanma oranına sahiptir (%71,4) (57). Travma sonucu optik sinirde kompresyon doğrudan hasara bağlı ödem ve vasküler yapıda spazma bağlı olarak iskemi ve enfarkt nedeniyle retina ganglion hücrelerinin ve sinir lifi aksonlarının hasarı sonucu oluşmaktadır (58). Optik sinir travması olan olgularda tipik olarak kafa travması öyküsü genelde vardır ve bu tanıda gecikmelere neden olabilir. Görme genellikle 1/10 civarında olup, diğer önemli bulgular relatif afferent pupil defektinin varlığıdır ve renk görme bozulmuştur. Erken dönemde papil ödem olabilir. Geç dönemde optik atrofi gelişir. Ancak ağır optik sinir hasarında bile papillanın başlangıçta normal görünümde olabileceği unutulmamalıdır. TON tedavisinde genellikle intravenöz yüksek doz (500-2000 mg/gün) steroidler kullanılır. Steroidin görme artışına katkıda bulunduğuna dair sağlam kanıtlar yoktur (59-60). Eritropoetin ile klinik TON

tedavisinde (üç gün boyunca günde 10.000-20.000 IU intravenöz enjeksiyon) pozitif nöroprotektif faydalar ve görme iyileşmesi bildirilmiştir (61). Başka bir araştırma da TON tedavisinde EPO'nun (2000 IU) intravitreal enjeksiyonuyla görme artışı ve görsel uyarılmış potansiyel cevaplarında artış saptanmış olup, intravitreal tedaviye rağmen bir yan etki gözlenmemiştir (62). Bu yıl yayınlanan ve metaanalizlerin sistematik incelemesinin yapıldığı bir çalışmada intravenöz metilprednizolon, eritropoetin ve levodopa-karbidopa kombinasyonunun üç randomize kontrollü çalışması da dahil edilmesine rağmen, herhangi bir tedavi için fayda kanıtı bulunamamıştır. Ek olarak, travmatik beyin hasarında yapılan büyük çalışmalar, megadoz metil prednizolon ile tedavi edilen hastalarda artan mortaliteye dair güçlü kanıtlar bulmuştur (63). Optik sinir dekompresyon cerrahisi hakkında yapılan çeşitli çalışmalarda, endikasyonlar şunlardır: İlerleyici görme kaybı (64), optik sinirin intrakranial segmentlerinde hasar veya avülsiyona dair kanıt eksikliği (64), VEP'te amplitüd azalması veya uzamış latans (65), steroid tedavisine yanıt vermeme (64) ve optik siniri sıkıştıran kemik parçalarının varlığı veya yakınında hematom olmasıdır (66). Tedavide dekompresyon için en uygun zaman travmadan bir hafta sonrasıdır (67). Mezankimal kök hücre tedavisi, mitoterapin (yani ekzojen mitokondriyal transplantasyonu), periferik sinir nakli, hipotermi ve lipit tedavileri üzerinde çalışılan ve umut vadeden yeni tedavi yaklaşımlarıdır (68).

Optik sinir avulsiyonu lamina cribrosa seviyesinden optik sinirin parsiyel veya tamamının ayrıldığı nadir bir durumdur. Genelde künt travma sonrası orbita içinde gerçekleşen anteroposterior çekiş optik sinirin ayrılmasına yol açacaktır (69). Görme kaybıyla sonuçlanan çok ciddi bir yaralanmadır. Klinik olarak vitreus hemorajisi, peripapiller hemoraji, geç dönemde diskte ekskavasyon ve pupil önünde vitreusa uzanan gliotik doku gözlenir. Optik sinir hasarı tam veya kısmi olabilir. Tam avülsiyonda, hasar genellikle optik kanal veya orbitada meydana gelir; sinirin intrakranial kısmı hareketliliği nedeniyle nadiren etkilenir (70). Hastanın optik sinir dekompresyonu veya yüksek doz steroidler gibi gereksiz tedavilere maruz kalmaması için tanının doğrulanması esastır (71). Hastalar, ftizis bulbi ve sekonder neovaskülarizasyon veya neovasküler glokom gibi komplikasyonlar açısından izlenebilir (72).

Travmatik göz yaralanmaları ve buna bağlı gelişen katarakt ve retinopatiler hala sıklıkla görülmektedir. Sık görülen bu patolojiler için her geçen yıl yeni tedavi modelleri ortaya çıkmakta ve bunlar oftalmoloji pratiğine dahil olmaktadır. Bu derlemede bu patolojiler genel anlamda tanımlanmış ve yeni bulgu ve tedavilere yer verilmiştir. Yeni tedavi yöntemlerinin geliştirilebilmesi için geniş serili yeni çalışmalara ihtiyaç vardır.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Will Machine Learning Take a Leading Role in Emergency Medicine Applications?

Acil Tıp Uygulamalarında Makine Öğrenimleri Başrolü Alır mı?

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Derleme | Review
Doi: https://doi.org/10.52827/hititmedj.1467697
Geliş Tarihi | Received: 12.04.2024
Kabul Tarihi | Accepted: 09.08.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Sezik S. Will Machine Learning Take a Leading Role in Emergency Medicine Applications? Hitit Medical Journal 2025;7(1):118-123. https://doi.org/10.52827/hititmedj.1467697

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Makale Derleme türünde olduğundan etik kurul onayına gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez SS Tasarım SS Veri Toplama/Veri İşleme SS Veri Analizi SS Makalenin Hazırlanması SS.
Hasta Onamı: Makale Derleme türünde olduğundan hasta onamına gerek yoktur..
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Ethical committee approval is not required.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: SS Design: SS Data Collection/Data Processing: SS Data Analysis: SS Manuscript Preparation: SS.
Informed Consent: Our University Clinical Research Ethics Committee has confirmed that no consent for publication from patients is required.
Financial Disclosure: There are no financial funds for this article.

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ABSTRACT

The main problems in the workflows of emergency services can be summarized as over-crowding, unnecessary usage trends and long waiting times. Emergency services experienced a breaking point during the pandemic, and new approaches regarding to management have come to the agenda. Health care providers around the world are looking to artificial intelligence as the solution to these challenges. applications into emergency department business processes. In the future, artificial intelligence-based machine learning models will be integrated to the clinical decision making support systems to reduce the workload of physicians, and also play an auxiliary role in the emergency services. In this article, we will discuss on the basis of the reasons that led to the combination of machine learning to summarize the current status of modeling in emergency services. It is brought to the fore that machine learning models enhance clinicians' decision-making abilities, reduce diagnostic errors, and alleviate cognitive load.

Keywords: Artificial Intelligent, ChatGPT, emergency department, machine-learning models.

ÖZET

Acil servislerde iş akışlarındaki temel problemler; yoğunluk, gereksiz kullanım eğilimleri ve uzun bekleme süreleri olarak özetlenebilir. Covid-19 pandemisi sırasında kırılma noktasını yaşayan acil servis yönetiminde yeni yaklaşımlar gündeme gelmiştir. Sağlık hizmeti sağlayıcıları, dünya çapında bu zorlukların çözümü olarak, yapay zekâ uygulamalarını acil servis iş süreçlerine dâhil etmeye başlamışlardır. Yapay zeka tabanlı makine öğrenimi modelleri, gelecekte klinik karar destek sistemlerine entegre edilerek hekimlerin iş yükünü azaltmalarının yanında acil servis işleyişleri için de yardımcı rol oynayacaklar gibi görünmektedir. Biz bu yazımızda, acil serviste makine öğrenimi birlikteliğine götüren nedenler temelinde modellemelerin acil servis hizmetlerindeki güncel durumu özetlemeye çalıştık. Makine öğrenimi modellerinin klinisyenlerin karar verme yetilerini geliştirdiği, tanısal hataları ve bilişsel yüklenmeyi azalttığı görüşleri öne çıkmaktadır.

Anahtar Sözcükler: Acil servis, ChatGPT, makine öğrenim modelleri, yapay zeka.

Giriş

Basit bir tanımla yapay zekâ, bilgisayarların görevleri tamamlamasına veya geleneksel anlamda tipik olarak insan zekâsı gerektirecek bilgi üretmesine odaklanan bilgisayar bilimi alanıdır. Yapay zekâ kapsamında makine öğrenimi (MÖ) ve derin öğrenme alanları bulunmaktadır. Teorik olarak MÖ, farklı sorun türlerinin çeşitli algoritmalar ile çözümlenmesini sağlarken yaşam kalitesini arttıran pratik çözümler üretir (1). Veri akışı sürekliliğinde, otomatik 'iyileştirme' veya "öğrenme" yeteneğine sahiptir. MÖ ve derin öğrenme ile büyük miktarlarda veri analiz edilir, özerk olarak varsayımlar üretilir. Klinik sonuçların daha doğru tahmin edilmesi sağlanır (2).

Acil Servis ve Makine Öğrenimi Birlikteliğine Götüren Nedenler

Mükemmel bir dünyada dahi, acil durumlarla başa çıkmaya hazırlıklı olmak çok önemlidir. Acil durumlar; herhangi bir zamanda, herhangi bir uyarı olmaksızın, en son teknolojiler kullanılıyor olsa bile ortaya çıkabilir. Acil durum yönetimi, çok sayıda aracı içeren senkronize bir faaliyettir (3). Dünya genelinde acil servis başvurularında nüfus artış hızından daha fazla bir artış olduğu gözlenmektedir (4). Acil olmayan nedenler ile başvuru, tekrar eden başvurular, yatış süresinde uzama, personel eksikliği gibi nedenler acil servislerde yoğunluğa neden olmaktadır (5). Bu yoğunluğun sonucu olarak mortalite, komplikasyon, tedavi bırakma, acil serviste kalış süresi, memnuniyetsizlik oranlarında artış gözlenmektedir. Acil servislerdeki iş akışının iyileştirilmesinin yanı sıra acil servis profesyonellerinin yeni yaklaşımlar ile bu iş akışlarını daha sistematik olarak düzenlemeleri yapay zekâ uygulamalarının gündeme gelmesini hızlandırmıştır (6). Bilgi teknolojisi çağında, sağlık alanında MÖ hasta süreçlerinin öngörüsü, elektronik sağlık kaydının otomatik olarak çıkarılması, dijital görüntülerin bütünleştirilmesi ve fizyolojik verilerin sürekli izlenmesi yoluyla tahmin modellerinin güncellenmesi gibi avantajlar sunmaktadır (7). MÖ modellerinin oluşturulması, acil serviste özellikle bazı durumlarda (sepsis, planlanmamış yoğun bakım ünitesine yatışlar, planlanmamış rekürren başvurular, vb.) öngörünün gelişmesine destek olmaktadır (8). Ayrıca, tahmin ediciler arasındaki yüksek dereceli, doğrusal olmayan etkileşimler ile daha kararlı tahminler yapılabilme avantajı da ortaya çıkmaktadır (9).

Acil Servis Hizmetlerinde Makine Öğrenimi Uygulama Alanları

Acil servislerde kaynak planlaması, iş yükünün tahmini ve yoğunluk yönetimi konularında matematiksel modelleme yöntemleri kullanılmaktadır (10). Hastaları taramak, katmanlaştırmak ve özelleşmiş tanılar koymak için MÖ temelli tanısal karar destek uygulamaları, tanısal modelleme sistemleri kullanılmaktadır. Bu araçların kullanılması yüksek düzeyde otomatikleştirilmiş sonuçlar için umut verici bir doğruluk göstermekte ve uygulanan model iyileştirmeye giden yolu göstermektedir (11). Yapay zekâ uygulamaları; tanısal görüntülemenin yorumlanmasında, hasta sonuçlarının tahmin edilmesinde ve hastanın yaşamsal belirtilerinin izlenmesinde (nabız hızı, kan basıncı, sıcaklık ve solunum takibi) umut verici sonuçlar ortaya koymuştur (12). MÖ modelleri, semptomları doğru bir şekilde değerlendirip sınıflandırarak, acil servise başvuran hastanın yaşam ile ölüm arasındaki çizgide aciliyet ve tedavi önceliğinin belirlenmesinde ilk değerlendirme olan acil durum seviyelerinin (triyaj) tahmin edilmesinde kullanılmaktadır (13). Acil servis triyajında yüksek riskli hastaları daha stabil hastalardan doğru bir şekilde ayırt etmek ve kesin kaynakları etkin bir şekilde kullanmak hedeflenmektedir (14). Bora ve ark. e-triyajda dört farklı makine öğrenmesi (Support Vector Machine (SVM), Kth Nearest Neighbor (KNN), Decision Trees, Random Forest) algoritmalarını değerlendirdikleri çalışmalarında Random Forest yaklaşımının daha iyi performans gösterdiğini rapor etmişlerdir (15). Goto ve ark. astım ve kronik obstrüktif akciğer hastalığı (KOAH) hastalarının triyajını kolaylaştırmak ve acil servis eğilimlerini (yoğun bakım, hastaneye yatış) tahmin etmek için dört MÖ yaklaşımları kullandıkları çalışmalarında en iyi performansın yoğun bakım için Boosting, hastaneye yatış için Random Forest yaklaşımlarının sağladığını belirtmişlerdir (16). Raite ve ark. geleneksel yaklaşımla (Emergency Severity Index (ESI)) karşılaştırıldığında, MÖ modellerinin (Lasso regression, random forest, gradient boosted decision tree, deep neural network) kritik bakım ve hastaneye yatış sonuçlarını tahmin etmek için üstün bir performans gösterdiğini rapor etmişlerdir (17).

Makine Öğrenimi Modelleme Yöntemleri

Başlıca MÖ yaklaşımları denetimli öğrenme, denetimsiz öğrenme ve yarı denetimli öğrenme

kategorisine girer. Denetimli öğrenme algoritmaları, eğitim verileri olarak bilinen tarihsel olarak etiketlenmiş bir veri kümesini kullanarak matematiksel bir model oluşturur. Ancak denetimsiz öğrenmede, veri kümesinin her kaydı için etiket mevcut değildir. Eğitim verileri ve denetimli öğrenme algoritmaları kullanılarak bir model geliştirilir. Daha sonra çıktı elde etmek amacıyla test verileri üzerinde girdiye dayalı tahmin test edilir (18). Denetimli öğrenme algoritmaları sınıflandırma ve regresyonu içerir (19). Bu alandaki en önemli algoritmalardan bazıları; lojistik regresyon, destek vektör makineleri (support vector machines - SVM), naive Bayes algoritması, karar ağaçları (Decision Trees), rastgele orman (Random Forest), gradyan artırma ve derin öğrenmedir. Elektronik sağlık kayıtlarında büyük miktarda verinin bulunması, tahmine dayalı modelleme için büyük ve karmaşık veri setlerinin kullanılmasına olanak sağlar. Tıbbi verilerin işlenmesinde popüler bir yaklaşım olan 'Lojistik Regresyon' algoritması ile ilk tahminleme için iyi sonuçlar elde edilir (20). Ancak bağımsız değişkenlerin gözlemlerden daha fazla olması durumunda lojistik regresyon yönteminin kullanımı mümkün olmayacaktır (21). Bu sorunu çözmek için etkili ve verimli değişken seçiminin yapılması gerekmektedir. Değişkenleri, hesaplanan önemlerine göre sıralamak için daha düşük tahmin hatasına sahip Random Forest kullanılabilir (22).

Logistic Regresyon: Verilerin eğrisine bir çizgi yerleştirerek değişkenler arasındaki ilişkilerin doğrusal bir modelini keşfeden bir MÖ algoritmasıdır. Sınıflandırma için de uygulanabilir.

Lasso Düzenlemeli Logistic Regresyon (Lasso Regresyonu): Regresyon katsayılarını sıfıra doğru küçülten, böylece önemli belirleyicileri etkin bir şekilde seçen ve modelin yorumlanabilirliğini artıran modellerden biridir (23).

Support Vector Machine (SVM): Yönetimi ve kullanımı kolay sınıflandırma algoritmasıdır. Bu algoritmada, bir veri öğesi olan her nokta 'n' boyutlu düzlem olarak bilinen uzayda boyutlu olarak çizilir. 'N' verinin özellik sayısını temsil eder. Sınıflandırma, farklı düzlemlerde bulunan veri kümesi noktalarının oluşturduğu sınıflardaki farklılaşmaya dayalı olarak yapılır. MÖ'nde tercih edilen ve kullanılan bu yöntem sıklıkla denetimli öğrenme problemlerinin çözümünde etiketlenmemiş veri miktarının fazla olduğu durumlarda verilerin gerçek zamanlı etiketlenmesi için sınıflandırılmasında tercih edilir. Basit bir doğrusal sınıflandırma olarak düşünülebilmesi için düşük boyutlu uzaydaki doğrusal olmayan problemin yüksek boyutlu bir uzayla eşleştirildiği yöntemdir. Küçük örneklem yönetimi için uygundur (24). Veriler için en iyi veri sınıflandırıcısını ayırt etmek için kullanılan bir algoritmadır. SVM çok iyi bir genelleme performansı elde edebilir.

Deep neural network model (Derin sinir ağı modeli), çoklu işlem katmanlarından oluşur. Sonuçlar, ara gizli birimler tarafından modellenir ve her gizli birim, doğrusal olmayan işlevlere dönüştürülen yordayıcıların doğrusal kombinasyonundan oluşur (9). Bir hücre ağının üretildiği ve hücreler arasındaki bağlantıların, elde edilen ağın eğitim verilerinin yapısını öğrenebileceği şekilde ayarlandığı yapay sinir ağı (ANN) adlı başka bir MÖ yöntemleri sınıfının bir parçasıdır. Genellikle, derin öğrenme yöntemindeki ağdaki katman sayısı, sıradan bir ANN'den çok daha yüksektir. Derin öğrenme, giriş verilerinden daha üst düzeyde çıkarılan özellikler içerir.

Kth Nearest Neighbor (KNN): KNN algoritması, sınıflandırılacak yeni bireyin yakınlığının önceki bireylerin k katı ile kontrol edildiği bir algoritmadır. Sınıflandırma sırasında test örnekleri, eğitim örnekleri kullanılarak birbirleriyle karşılaştırılır. Yakınlık aralığının değerlendirilmesinde Öklid mesafesi kullanılır. Tahminler, komşu örneklerin çoğunluk oylamasına dayanmaktadır. Yüksek k değerlerine uyma eğiliminde olduğu için dikkatli olunmalıdır (25).

Decision Trees (Karar Ağaçları): Karar ağaçları sadece kararları göstermekle kalmaz, aynı zamanda kararların açıklamalarını da içerir. Karar ağacını oluşturan eğitim süreci tümevarımsaldır. Bir dizi eğitim nesnesinden bir karar ağacı oluşturma prosedürüne 'tree induction' denir. Bu yöntemi, kendini keşfetmenin en yaygın yöntemlerinden biridir. Sınıflandırma veya tahmin amacıyla kullanılabilecek ağaç benzeri kalıpları keşfetmeye hizmet eder.

Karar ağaçları, bilgi keşfi sırasında çeşitli testler yaparak hedefi tahmin etmek için en iyi sırayı bulmaya çalışır. Her test karar ağacında dallar oluşturur ve bu dallar başka testlerin yapılmasına neden olur. Bu işlem, test işlemi bir yaprak düğümünde bitene kadar devam eder. Kökten hedef yaprağa giden yola, hedefi sınıflandıran "kural" denir. Kurallar "eğer öyleyse" modelini yansıtır (26). Karar ağacı, ağaç benzeri

yapıları kullanarak verileri eşlemek, çıktıya alınacak kararları sınıflar veya sınırlar olarak sınıflandırmak için kullanılan başka bir algoritmadır.

Gradyan artırılmış karar ağacı: Önceki modellerin hatalarını ve artıklarını tahmin eden yeni ağaç modelleri oluşturan bir topluluk yöntemidir. Bu model, yeni modelleri eklerken, bir kayıp işlevini en aza indirmek için gradyan alçalma algoritması kullanır (27).

Random Forest: Denetimli bir öğrenme algoritması olan rastgele orman algoritması, sınıflandırma ve regresyon görevlerinde kullanılır. Rastgele orman algoritması, birden fazla karar ağacı oluşturur ve daha doğru ve istikrarlı bir tahmin elde etmek için bunları birleştirir. Birkaç rastgele karar ağacını birleştiren ve tahminlerinin ortalamasını alan yaklaşım, değişken sayısının gözlem sayısından çok daha büyük olduğu ortamlarda daha iyi performans gösterir (28).

Yöntem bankacılık, ticaret, sağlık gibi birçok alanda kullanılmaktadır. Sağlık alanında, tıpta doğru bileşen kombinasyonunu belirlemek, hastalıkları belirlemek ve hastanın tıbbi kayıtlarını kullanarak hastanın tıbbi geçmişini analiz etmek için kullanılır. Rastgele orman sınıflandırıcısı, her sınıflandırıcının, giriş vektöründen bağımsız olarak örneklenen rastgele bir vektör kullanılarak oluşturulduğu ve her ağacın bir giriş vektörünü sınıflandırmak için en popüler sınıfa tek birim oy verdiği ağaç sınıflandırıcılarının bir kombinasyonundan oluşur. Bir karar ağacının tasarımı, bir nitelik seçim ölçüsünün ve bir budama yönteminin seçilmesini gerektirir. Karar ağacı çıkarımı için kullanılan öz niteliklerin seçiminde birçok yaklaşım vardır ve çoğu yaklaşım, özniteliğe doğrudan bir kalite ölçüsü atar. Karar ağacı indüksiyonunda en sık kullanılan nitelik seçim ölçüleri Information Gain Ratio (29) ve Gini Endeksi (30).

Acil Servis Uygulamalarında Makine Öğreniminin Geleceği ve Uygulamada Olası Engeller

MÖ modelleri, bilgiyi kodlayan sabit kurallara dayalı kararların alındığı geleneksel modeller ile ulaşılması zor olan, ölçeklenebilirliği gerçekleştirirler. MÖ yaklaşımlarının klinik karar verme yeteneklerini daha da ilerletmek için vazgeçilmez yeni nesil yardımcı teknoloji olacaktır (31). Yeterli klinik kanıt ve uygun bir düzenleyici çerçeve olduğu varsayıldığında, yapay zekânın etkin bir şekilde kullanılmasında dijital teknolojiye geçiş temelli olası engeller olabileceği de göz önünde bulundurulmalıdır. Elektronik tıbbi kayıtların doğru, tam zamanlı ve eksiksiz alınması gerekli olup bu kayıtların mevcut klinik iş akışına entegrasyonunun sağlanması önemlidir.

Yapay Zekâ ve Etik Sorunsalı

İnsan gibi düşünüp yorumlayan, muhakeme eden ve sonuçlar çıkaran yapay zeka uygulamalarının tabii ki etik sorunları da vardır. Belki de bu sorunlar yapay zeka uygulamalarını bir müddet daha güncel hayatımıza girmekten uzak tutacaktır. Bunların en başında bu kadar verinin bulunduğu hasta kayıtlarının istenildiği zaman ve miktarda sağlık personelince görülüyor olması hasta mahremiyeti açısından çok ciddi bir sorundur. Anayasal güvence altında olan sağlık hakkının bu uygulamaları kullanmayan kişilerce eşitsizlik olarak kabul edilebilecek olması, sağlık personeli ve bireylerin bu uygulamalara uyum sağlayamamasının getireceği karmaşık durumda sorunlardan bazılarıdır. Belki de en ciddi sorun bu uygulamalardan dolayı ortaya çıkabilecek zararların muhatabı kim olacak; Uygulayan sağlık profesyonellerimi yoksa üretici şirketler mi?

Sonuç

Acil servis verileri kullanılarak oluşturulan MÖ modellemelerine talep artmaktadır. Bu modellemeler klinisyenlerin, zamanında ve doğru klinik bakım ile optimal kaynak kullanımı konularındaki karar verme yetilerini geliştirirler, tanısal hataları ve bilişsel yüklenmeyi azaltırlar. Yapay zekâ tabanlı tahmin uygulamasının iyi olması, klinisyenlerin MÖ algoritmasının doğruluğuna güvenebilmesinin anahtarıdır (32). Sağlık alanında yapay zeka konusunda çalışanların, denetimsiz modellerden daha çok yorumlanabilir modeller geliştirmesi, yarı denetimli MÖ modellemesi oluşturması, bakım standardı veya klinik kararları karşılaştıran çalışmalar yapması beklenmektedir. Yakın gelecekte, bir zamanlar sağlık çalışanları tarafından yürütülen görevleri daha fazla yapay zekânın üstlendiği ve insan beyni ile yapay zekâ uyumunun sağlandığı görülebilecektir.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

ERAS Protocol and Evidence-Based Practices in Postoperative Care and Management of Patients with Ovarian Cancer Undergoing Hyperthermic Intraperitoneal Chemotherapy Procedure After Cytoreductive Surgery

Sitoredüktif Cerrahi Sonrası Hipertermik İntraperitoneal Kemoterapi Prosedürü Uygulanan Over Kanserli Hastanın Postoperatif Bakım ve Yönetiminde ERAS Protokolü ve Kanıta Dayalı Uygulamalar

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Derleme | Review
Doi: https://doi.org/10.52827/hititmedj.1512983
Geliş Tarihi | Received: 09.07.2024
Kabul Tarihi | Accepted: 13.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Temiz M, Küçükkaya B. ERAS Protocol and Evidence-Based Practices in Postoperative Care and Management of Patients with Ovarian Cancer Undergoing Hyperthermic Intraperitoneal Chemotherapy Procedure After Cytoreductive Surgery. Hitit Medical Journal 2025;7(1):124-136. https://doi.org/10.52827/hititmedj.1512983

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Makale Derleme türünde olduğundan etik kurul onayına gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez MT, BK Tasarım MT, BK Veri Toplama/ Veri İşleme MT, BK Veri Analizi MT, BK Makalenin Hazırlanması MT, BK.
Hasta Onamı: Makale Derleme türünde olduğundan hasta onamına gerek yoktur..
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.
Telif Hakı & Lisans: Dergi ile yayın yapan yazarlar, CC BY-NC 4.0 kapsamında lisanslanan çalışmalarının telif hakkını elinde tutar.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Ethical committee approval is not required.
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: MT, BK Design: MT, BK Data Collection/Data Processing: MT, BK Data Analysis: MT, BK Manuscript Preparation: MT, BK.
Informed Consent: Our University Clinical Research Ethics Committee has confirmed that no consent for publication from patients is required.
Financial Disclosure: There are no financial funds for this article.

ERAS Protocol and Evidence-Based Practices in Postoperative Care and Management of Patients with Ovarian Cancer Undergoing Hyperthermic Intraperitoneal Chemotherapy Procedure After Cytoreductive Surgery

ABSTRACT

A post-surgical accelerated recovery protocol is a multifaceted set of evidence-based guidelines for the appropriate treatment and care of patients. This protocol is incorporated into management processes after many different major surgeries, including surgery for gynecologic cancers such as ovarian cancer. Postoperative monitoring and care is of great importance, especially in procedures with a high risk of complications such as hyperthermic intraperitoneal chemotherapy after cytoreductive surgery. Especially in patients undergoing this procedure, components of the postoperative accelerated recovery protocol such as avoiding unnecessary nasogastric tube administration, prevention of ileus, multimodal analgesia, early oral intake, monitoring of blood glucose levels, thromboprophylaxis, early mobilization, prevention of nausea and vomiting are of great importance. In this direction, it is recommended that women's health nurses should include the postoperative accelerated recovery protocol and evidence-based practices in nursing care and management processes and conduct scientific studies with high level of evidence in providing holistic care to the patient after hyperthermic intraperitoneal chemotherapy after cytoreductive surgery. This review aims to traditionally review the postoperative accelerated recovery protocol, evidence-based practices, and the roles and responsibilities of nurses in the postoperative care and management of ovarian cancer patients undergoing hyperthermic intraperitoneal chemotherapy procedure after cytoreductive surgery.

Keywords: Cytoreductive surgery, ERAS, evidence-based practices, hyperthermic intraperitoneal chemotherapy, ovarian cancer.

ÖZET

Cerrahi sonrası hızlandırılmış iyileşme protokolü, hastaların uygun şekilde tedavi ve bakımının sağlanabilmesi için hazırlanan çok yönlü kanıta dayalı uygulamaların yer aldığı kılavuzlardır. Bu protokol, over kanseri gibi jinekolojik kanserlerin cerrahisi de dâhil olmak üzere birçok farklı majör cerrahi sonrasındaki yönetim süreçlerine dâhil edilmektedir. Özellikle sitoredüktif cerrahi sonrası hipertermik intraperitoneal kemoterapi gibi komplikasyon riskinin yüksek olduğu işlemlerde postoperatif izlem ve bakım büyük öneme sahiptir. Özellikle, bu işlemin uygulandığı hastalarda, gereksiz nazogastrik tüp uygulamasından kaçınılması, ileusun önlenmesi, multimodal analjezi uygulanması, erken oral alım, kan glikoz değerinin izlemi, tromboprofilaksi, erken mobilizasyon, bulantı ve kusmanın önlenmesi gibi cerrahi sonrası hızlandırılmış iyileşme protokolü bileşenleri büyük önem taşımaktadır. Bu doğrultuda, kadın sağlığı hemşirelerinin, sitoredüktif cerrahi sonrası hipertermik intraperitoneal kemoterapi sonrası hastaya bütüncül bakım vermede cerrahi sonrası hızlandırılmış iyileşme protokolünü ve kanıta dayalı uygulamaları hemşirelik bakım ve yönetim süreçlerine dahil edilmesi ve kanıt düzeyi yüksek bilimsel çalışmalar yapması önerilmektedir. Bu derlemede, sitoredüktif cerrahi sonrası hipertermik intraperitoneal kemoterapi prosedürü uygulanan over kanserli hastanın postoperatif dönemde bakım ve yönetiminde cerrahi sonrası hızlandırılmış iyileşme protokolü, kanıta dayalı uygulamalar ile hemşirelerin rol ve sorumluluklarını geleneksel olarak derlemektir.

Anahtar Sözcükler: ERAS, hipertermik intraperitoneal kemoterapi, kanıta dayalı uygulamalar, over kanseri, sitoredüktif cerrahi.

Giriş

Dünyada ve ülkemizde görülen jinekolojik kanserlerden biri olan over kanseri yüksek mortalite oranına sahiptir. 2022 yılında 324603 kişi yeni over kanseri tanısı almış; 206956 kişi ise bu kanser nedeniyle yaşamını yitirmiştir. Ayrıca kadınlarda görülen kanser türlerinin mortalite oranları sıralamasında over kanseri 8.sırada yer almaktadır (1). Over kanserinin uzun süre belirti vermemesi ve genelde gastrointestinal sistem kaynaklı gibi görünen belirtilere sahip olması nedeniyle kesin tanının belirlenmesi, kanserin metastaz yaparak ilerlediği ileri evrelerde mümkün olabilmektedir. Kadınların yaklaşık %70'ine, yüksek postoperatif morbidite ve daha kötü prognoz ile ilişkili olan ilerlemiş hastalık (FIGO evre > II, yani pelvis dışına uzanan tümör) tanısı konulabilmektedir. Tanı anında bölgesel veya uzak hastalık durumunda beş yıllık sağkalım oranı %40'ın altında seyretmektedir (2). Bu nedenle over kanserinde hem cerrahi hem de tıbbi ortamda tedavi stratejilerini iyileştirme ve hastanın prognozunu olumlu yönde etkileme çabaları sürekli olarak devam etmektedir. Bu amaçla uygulanan cerrahi prosedürlerden biri de sitoredüktif cerrahiyi takiben uygulanan hipertermik intraperitoneal kemoterapi (SRCHİPEK) işlemidir.

Sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi, hem primer periton kanserleri hem de kolorektal, apendiks, over, mide ve diğer malignitelere sekonder periton metastazı olan peritoneal yüzey maligniteleri için uygulanan kapsamlı bir tedavi seçeneğidir. Sitoredüktif Cerrahi (SRC), görünür tümörlerin peritoneal yüzeylerden ve abdomino-pelvik organlardan cerrahi olarak çıkarılmasını içermektedir. Bu cerrahi, tek bir peritoneal nodülün eksizyonundan çoklu viseral rezeksiyonlara ve anastomozlara kadar geniş bir spektrumu kapsamaktadır. Bu işlemi, 41°C - 43°C'ye kadar ısıtılmış olan yüksek konsantrasyonlu kemoterapi ajanlarının (sisplatin, mitomisin) periton boşluğuna pompalanmasını içeren Hipertermik İntraperitoneal Kemoterapi (HİPEK) işlemi takip etmektedir. HİPEK kapalı veya açık karın teknikleri ile yapılabilmekle birlikte, kapalı HİPEK'in avantajları karın içi basıncın artarak doku penetrasyonunun artması ve ısı kaybının önlenmesi iken, açık HİPEK'in avantajı kemoterapötik ilaçların daha homojen dağılmasına olanak vermesidir. Ameliyat süresi sekiz ila on beş saat arasında değişebilmekle birlikte primer hastalık ve kurumsal protokol, çeşitli enstitülerde farklılık gösterebilmektedir (3).

SRCHİPEK, avantajlı sağkalım sonuçlarına sahip olması nedeniyle peritoneal yüzey maligniteleri için bir tedavi standardı haline gelmiştir. Ancak bu komplike prosedür, postoperatif erken ve geç dönemde yaşamı tehdit eden bazı komplikasyonları da beraberinde getirmenin yanı sıra, işlem sonrası görülen majör komplikasyon oranlarının %51'e kadar çıktığı bildirilmektedir (4). İşlemin uzun sürmesi, büyük miktarda sıvı, protein ve kan kaybına yol açması, vücut normotermisini ve normoglisemisini etkilemesi, işlem sırasında kullanılan sisplatin gibi kemoterapik ajanların nefrotoksik etkileri nedeniyle akut böbrek hasarına yol açabilmesi, tüm vücut sistemlerini etkileyen patofizyolojik değişiklikler sonucunda homeostazın bozulması işlem sonrasında mortalite ve morbidite oranlarını artıran etkenlerdir. Bu faktörler, cerrahi müdahale sonrası komplikasyon risklerini yükseltmekle birlikte, hastanın genel sağlık durumu üzerinde olumsuz etkilere yol açabilmektedir. Rapor edilen verilere göre, bu işlemi geçiren hastalarda morbidite oranı %12-60, mortalite oranı ise %0,9-5,8 arasında değişmektedir (5). Literatür incelendiğinde hastalarda bu işlemden 90 gün sonra bile komplikasyon geliştiği görülmektedir (3). Bu bağlamda, kompleks bir işlem olan bu cerrahinin odak noktası, postoperatif patofizyolojiyi ve yönetimini anlamak, komplikasyonları erken dönemde saptayarak morbiditeyi azaltmak ve sağkalımı artırmak için uygun tedavi ve bakım yöntemlerini uygulamaktır. Bu doğrultuda, SRCHİPEK işlemi uygulanan hastaların postoperatif bakım ve yönetim süreçlerine dahil edilebilecek uygulamalardan birisi olan ve kanıta dayalı çalışmalar doğrultusunda hazırlanan cerrahi sonrası hızlandırılmış iyileşme protokolleri (ERAS) büyük önem taşımaktadır. SRCHİPEK işlemi gibi patofizyolojik değişimlerin ve postoperatif komplikasyonların sıklıkla görüldüğü majör cerrahilerde ERAS protokolüne uyum sağlanmasıyla komplikasyon oranının %33'ten %21'e gerilediği ve dolayısıyla hastanede kalış süresinin 13,5±9,5 günden 8,6±4,9 güne düştüğü görülmektedir (6).

ERAS protokolleri, ameliyat sonrası bakımı standartlaştırmayı ve optimize etmeyi ve dolayısıyla majör cerrahi sonrası olumsuz sonuçlarla bağlantılı olarak ortaya çıkan aşırı postoperatif metabolik ve

inflamatuar yanıtı modüle etmeyi amaçlamaktadır (7). Yüksek derecede uyum ile birlikte ERAS prosedürlerinin uygulanması hastada ortaya çıkabilecek komplikasyonları, hastanede kalış süresini ve maliyetleri önemli ölçüde azalttığı gösterilmiştir. İlk olarak kolon rezeksiyonunda gösterilen ERAS protokolleri, sonrasında benzer tekrarlanabilir faydaları olan çok sayıda gastrointestinal sistem ve diğer büyük cerrahi prosedürlere uygulanmıştır (8). Artan talep nedeniyle, birden fazla cerrahi alt uzmanlık için özel ERAS kılavuzları yayınlanmış ve güncellenmiştir ve kılavuz geliştirme sürecini ve metodolojisini standartlaştırmak ve optimize etmek için güncel öneriler yayınlanmıştır (9). SRCHİPEK işlemine özgü olarak hazırlanan ERAS kılavuzlarında birçok jinekolog, onkolog ve anestezist yapılan çalışmaları inceleyerek panel ortamında kanıtlar değerlendirilerek öneriler paylaşılmıştır (10). Kadın sağlığı alanında hem obstetrik hem de jinekolojik operasyonlarda kullanılmak üzere hazırlanmış ERAS kılavuzları bulunmakla birlikte, Amerikan Kadın Doğum Uzmanları ve Jinekologlar Koleji (ACOG), kadınların preoperatif ve postoperatif sağlık düzeylerini yükseltilmesi, komplikasyonların azaltılması ve cerrahi işlemler sonrası görülen mortalite ve morbidite oranlarını azaltmak amacıyla ERAS protokollerinin tedavi ve bakım süreçlerine entegre edilmesini önermektedir (11).

Bu derlemede amaç, sitoredüktif cerrahi sonrası hipertermik intraperitoneal kemoterapi prosedürü uygulanan over kanserli hastanın postoperatif dönem yönetiminde kanıta dayalı uygulamalar ve ERAS protokolü kapsamında hemşire rol ve sorumluluklarını geleneksel olarak derlemektir.

SRCHİPEK Prosedüründe Postoperatif Dönem Nazogastrik (Ng) Sonda Uygulaması

Abdominal cerrahi sonrası nazogastrik tüp ile midenin rutin dekompresyonunun hasta üzerindeki etkisi uzun süredir tartışılmaktadır. SRCHİPEK uygulanan hastalar, yaygın intraoperatif barsak manipülasyonu, adezyonların parçalanması, intraoperatif sıvı resüsitasyonu, hipertermi ve kemoterapinin ileus üzerindeki ilave etkileri nedeniyle barsak fonksiyonlarının normale dönüşünde zorlanabilmektedir. SRCHİPEK işlemi sırasında sıklıkla barsak rezeksiyonları ve anastomoz gibi girişimler bağırsakların cerrahi sonrası normale dönüş süresini olumsuz etkilemektedir (10).

3964 hastayı dâhil eden 26 çalışmanın incelendiği bir meta analiz sonuçlarına göre NG tüp kullanılmayan hastalarda pnömoni ve atelektazi görülme oranı azalmış ve oral alıma geçiş süresi kısalmıştır. NG tüp kullanılmayan hastalarda bulantı daha fazla görülürken bu durumun hastanede kalış süresini etkilemediği belirlenmiştir (12). NG tüp kullanan ve kullanmayan hastaların kıyaslandığı ve 5240 hastayı içeren 33 çalışmanın dâhil edildiği bir Cochrane incelemesinde ise NG tüp uygulanan hastalarda daha fazla pulmoner komplikasyonun geliştiği, barsak fonksiyonlarının normale dönme süresinin ve hastanede kalma süresinin uzadığı sonuçlarına ulaşılmıştır. Ayrıca NG tüp kullanıldığında daha az bulantı şikâyeti görülmekle birlikte hastalarda rahatsızlık hissi gelişmesine neden olmaktadır (13). Benzer şekilde, 17 randomize kontrollü çalışmanın incelendiği bir meta-analizi sonuçları ise, NG tüp dekompresyonunun gastrointestinal fonksiyonun daha erken sürede normale dönmesi ve postoperatif komplikasyonların azaltılması gibi herhangi bir klinik fayda sağlamadığını göstermiştir (14). Rao ve ark.'nın (2011) toplam 1416 hastayı içeren 7 çalışmanın incelediği meta-analizde, rutin NG tüp kullanımının gastrointestinal fonksiyonun normale dönme süresini azaltmadığını aksine farengolarenjit ve solunum yolu enfeksiyonunu insidansını artırdığı sonucuna ulaşılmıştır (15).

ERAS protokolüne göre ise; mide boşalmasında gecikme riskinin olduğu durumlar dışında barsak motilitesini olumsuz etkilediği ve postoperatif komplikasyonları artırdığı için NG tüp rutin olarak uygulanmamalıdır (Orta Kanıt Düzeyi, Güçlü Öneri) (10).

NG uygulanması gereken durumlarda ise hastanın yeterli bir şekilde bilgilendirilmesi hemşirenin sorumluluklarındandır. Hastaya bu işlemin neden uygulandığı ayrıntılı bir şekilde anlatılmalıdır. NG tüp takıldıktan sonra ise aspirasyon gelişimini önlemek için hastanın yatak başı 30-45 derece yükseltilmelidir (16). Hasta bu işlemden sonra ağız solunumu yapacağından oral mukoza kurumasına bağlı gelişebilecek komplikasyonların önlenmesi için ağız bakımı ve odanın nemli tutulması önemlidir. Tüpün gastrointestinal kanala yapışmasını önlemek amacıyla günde bir kez kendi ekseni etrafında döndürülmesi

gerekmektedir. Aynı zamanda NG tüpünün sebep olacağı basınç yaralanmalarını gözlemlemek ve önlemek hemşirenin sorumluluklarından bazılarıdır (17).

Üriner Sonda Uygulaması

SRCHİPEK işleminde gerçekleşen patofizyolojik olaylar sonucunda büyük hacimli sıvı kayıpları meydana gelebilmektedir. Bu durumda yeterli organ perfüzyonunu sürdürmek için uygulanan sıvı tedavisi ile aşırı sıvı yüklenmesi gibi yan etkiler ortaya çıkabilmektedir. Ayrıca işlemin HİPEK fazında kullanılan ve nefrotoksik etkileri olan sisplatin gibi ajanlar böbrek hasarına neden olmaktadır. Gelişen hipoperfüzyon ve akut böbrek hasarının üriner çıktıya etkisini değerlendirmek için üriner kateter uygulaması sıklıkla tercih edilmektedir. Ancak kalıcı ve uzun süreli üriner sonda uygulamasının idrar yolu enfeksiyonu ve deliryum gibi yan etkileri bulunmaktadır. Yapılan bir çalışma uzun süreli üriner kateter uygulanan hastaların %3-5'inde idrar yolu enfeksiyonu (18) görüldüğü ve yoğun bakım ünitesindeki hastaların %30'unda ise deliryum geliştiği sonuçlarına ulaşmıştır. Bu yan etkilerin görülme oranı kateter uygulandıktan sonraki 48 saatte artış göstermektedir (19). Yapılan büyük bir gözlemsel çalışmada, kolorektal cerrahide idrar retansiyon oranları (%14) belirlenmiş ve erkek cinsiyet ve postoperatif epidural analjezi ortaya çıkan retansiyonun önemli bağımsız belirleyicileri olarak nitelendirmiştir (20).

- Üriner kateterin en geç postoperatif 3.gün sabah çıkarılması gerekmektedir (Orta Kanıt Düzeyi, Güçlü Öneri) (10).
- Epidural kateter çıkarılmadan önce idrar sondasının çıkarılması yöntemi uygulanabilir (Orta Kanıt Düzeyi, Zayıf Öneri) (10).

Postoperatif İleusun Önlenmesi

SRCHİPEK, tüm abdomenin eksplorasyonunu, ince bağırsağın kapsamlı manipülasyonunu ve sıklıkla kolorektal rezeksiyon ve anastomozlar dâhil olmak üzere birkaç viseral rezeksiyonu gerektiren majör bir cerrahi prosedürdür. Bir metaanaliz sonuçlarında, elektif kolon cerrahisini takiben uzamış postoperatif ileus insidansı %10,2 olarak belirlenmekle (21) birlikte bu oranın hipertermik solüsyon kullanımı, kemoterapik ajanlar ve peritonenal karsinomatozun ek etkileri ile daha da yükselebileceğini vurgulanmaktadır (22). SRCHİPEK prosedürü sırasında yapılan majör işlemler sonucunda abdominal apse oluşumu, hemoraji, pankreatit, paralitik ileus, diyare ve anastomoz kaçağı gibi gastrointestinal sistem komplikasyonları gelişebilmektedir. Bu komplikasyonlar arasında yer alan paralitik ileus işlem sırasında karın içine verilen hipertermik solüsyon ve peritoneal maligniteye bağlı olarak ortaya çıkmakta ve postoperatif dönemde en sık karşılaşılan morbidite nedenini oluşturmaktadır (3). Torakal epidural analjezi, ameliyat sonrası dönemde prokinetik ajanların ve laksatiflerin kullanımı, kahve tüketimi ve şekersiz sakız çiğneme ile erken mobilizasyon gibi uygulamaların barsak fonksiyonlarının normale dönmesi için kullanımı önerilmektedir (10).

Epiduralların postoperatif ağrı kontrolünü iyileştirdiği ve sitoredüktif cerrahi sonrasında görülebilen ileus oranlarını azalttığı gösterilmiştir (23). Daha önceki çalışmalar epidural lokal anesteziklere belirgin bir fayda göstermemiş olsa da, 2016 yılında yapılan büyük bir Cochrane incelemesinde, 8754 hasta ile yapılan 128 çalışmayı değerlendirilmiştir. Değerlendirme sonuçlarına göre, hastaların işlemden sonra ilk bağırsak hareketine kadar geçen sürenin kısaldığı ve postoperatif ağrı seviyelerinin azaldığı belirlenmiştir (24). Bununla birlikte, orta torasik epidurallar ve foley kateterlerin varlığı hastanın mobilizasyonunu engelleyebileceğinden transvers abdominis plan (TAP) blok kullanımı artmıştır. Sitoredüktif cerrahiyi incelemek için yapılan iki küçük çalışma, TAP bloklarının daha düşük idrar retansiyon oranlarına ve daha kısa hastanede kalış süreleri ile ilişkili olduğu, ancak ağrı değerlendirme puanlarının epidurallere göre daha yüksek olduğunu göstermiştir (25). Nazogastrik tüplerden kaçınma, erken oral beslenme ve mobilizasyon gibi diğer ERAS müdahaleleri postoperatif ileusu azalttığı görülmektedir (26).

Aynı zamanda NG sonda kullanımından kaçınma, erken oral beslenme ve erken mobilizasyon gibi ERAS müdahaleleri ile paralitik ileus görülme oranının azaldığı belirtilmektedir (27). 2016 yılında yapılmış ve 8754 hastanın yer aldığı 128 çalışmayı içeren bir Cochrane incelemesinde epidural analjeziklerin etkili ağrı yönetimi sayesinde hastanın postoperatif dönemde barsak motilitesinin normale dönme süresinde kısalma olduğu sonucuna ulaşılmıştır (28). Jinekolojik cerrahiler sonrası gelişen ileus oranlarının

kahve tüketimi ile %30'dan %10'a düştüğü ve sitoredüktif cerrahide barsak motilitesini hızlandığı belirtilmektedir (29). Ancak SRC üzerine yapılan başka bir çalışmada kahve tüketimi olmayan hastalarda ilk barsak motilitesi süresinin daha kısa olduğu sonucuna ulaşılmıştır (30). Bu nedenle postoperatif ileusu önleme kafein tüketimi konusu tartışmalıdır. Ayrıca 205 yılında yapılan ve 81 çalışmanın değerlendirildiği bir Cochrane incelemesinde ameliyat sonrası barsak motilitesini hızlandırmak ve gaz çıkışını sağlamada şekersiz sakız çiğnemenin etkili olduğu bildirilmiştir (31). Topçu ve Öztekin 2016 yılında yaptıkları bir randomize kontrollü çalışma sonucunda sakız çiğneme uygulamasının hastalarda görülen paralitik ileus, gaz çıkışı ve defekasyon süresini kısalttığı sonucuna ulaşılmıştır (32). Yapılan bir başka randomize kontrollü bir çalışmada, sakız çiğnemenin ve laksatif kullanımının postoperatif dönemde gastrointestinal fonksiyonların normale dönüş süresini 1 gün, ileus gelişimini ise %15-36 oranında azalttığını göstermektedir (33). Terzioğlu ve arkadaşlarının yaptığı bir çalışmada sakız çiğneme ile distansiyon ve konstipasyon gelişiminin azaldığı ve dolayısıyla hastane kalış süresinin azalırken hasta memnuniyetinin arttığı sonuçları diğer çalışmaları destekler niteliktedir (34).

- Postoperatif ileusu önlemek için SRCHİPEK işleminin ardından 72 saat lokal anestezikler ve kısa etkili opiodleri içeren torasik epidural analjezi (TEA) önerilmektedir (Düşük Kanıt Düzeyi, Güçlü Öneri) (10).
- Postoperatif ileusu önlemek için şekersiz sakız çiğneme, kahve tüketme, laksatif ve prokinetik ajanlar gibi uygulamalar birlikte ya da tek başına endike olabilir (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).

Postoperatif Ağrı Yönetimi

İdeal bir analjezi ile

- Etkili ağrı yönetimi sağlanmalı
- Erken mobilizasyona olanak sağlanmalı
- Herhangi bir komplikasyon gelişmemeli
- Erken oral alıma izin vermeli
- Barsak fonksiyonun geri dönme süresine olumlu etkileri olmalıdır (35).

HİPEK işleminin dâhil edildiği ya da edilmediği neredeyse tüm sitoredüktif cerrahilerde sıklıkla orta hat lapatoromi insizyonu tercih edilmektedir. SRCHİPEK'te en uygun analjezik prosedür için kanıt sağlayan prospektif veya randomize kontrollü bir çalışma yoktur. Bu nedenle, öneriler retrospektif vaka serisi analizi, uzman görüşü ve diğer büyük karın içi ameliyatlardan elde edilen kanıtlardan elde edilmektedir.

TEA, laparotomi işlemi sonrası, bağırsak fonksiyonunun iyileşmesine yardımcı olması, anastomozların stabilitesini sağlaması ve pulmoner komplikasyon oranlarını azaltması nedeniyle tercih edilen en etkili teknik olarak kabul edilmektedir. Tek merkezli bir retrospektif analiz, hasta kontrollü opioid analjezi opioidlerine kıyasla TEA kullanıldığında HİPEK sonrası sağkalımın daha iyi olduğunu bildirmektedir (36).

Kısa etkili bir opiat ile birlikte düşük dozda lokal anestezik konsantrasyonlarının kullanılması, sempatik blokaja bağlı motor blok ve hipotansiyon riskini en aza indirirken en iyi analjezi kombinasyonunu sunmaktadır (37). Epidural aile ağrı yönetiminde hedef kateterin ameliyat sonrası 48-72 saat için çıkarılması olmalıdır. Hematom ve apselerden kaynaklanan lezyonlarıın yol açtığı ağrı ve hipotansiyon (hem sıvılar hem de vazoaktif destek kullanılarak) nörolojik izleme yönetimi gibi prosedürlere uyulması önem taşımaktadır.

Multimodal analjezi, analjezik ilaçların nonfarmakolojik yöntemlerin birbiriyle yarattığı sinerjik etkiden faydalanılarak ağrı yönetiminin sağlanmasıdır. Bu analjezik yöntemler kombine halde ve düşük dozlarda verilmektedir ve böylece yan etkileri de azaltılabilmektedir. Ketamin gibi analjeziklerin halüsinasyon, taşikardi ve hipotansiyon gibi yan etkilerinin olması ve multimodal analjezi yaklaşımında kullanılan invaziv yöntemlerde kanama riskinin bulunması nedeniyle hemşirenin hastayı dikkatli bir şekilde izlemesi önemlidir (38).

- Postoperatif analjezi için intravenöz opioidlere seçenek olarak SRCHİPEK işlemi sonrası en az 72 saat lokal anestezik ± kısa etkili opiat içeren torasik epidural analjezi (TEA: T5-11) önerilmektedir (Yüksek Kanıt Düzeyi, Güçlü Öneri) (10).
- TEA sonlandırıldıktan sonra parasetamol, NSAİİ ve opioidler kullanılabilir (Yüksek Kanıt Düzeyi, Güçlü Öneri) (10).
- Diğer alternatif analjeziklerin (ketamin, lidokain, gabapentin) önerilmemektedir (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).

Hemşireler multimodal analjezi yolu ile ağrı yönetiminde multidisipliner ekip içerisinde önemli

bir yere sahiptir. Hasta için hazırlanan tedavi planına katılım sağlamakta ve tedavi sürecinde hastada ortaya çıkan fizyolojik ve davranışsal yanıtın takibini yapmaktadırlar. Bu yüzden uygulanacak analjeziklerin sınıflandırmalarını, etki mekanizmalarını, farmakokinetik özelliklerini ve diğer ilaçlarla olan etkileşimlerini çok iyi bilmelidirler (39). Hastanın yaşına, bilinç durumuna ve uygulanan cerrahi prosedüre uygun olarak geçerli bir ağrı skalası ile değerlendirme yapılmalıdır. Ağrının nedeni, artıran ya da azaltan faktörleri, yeri, tipi ve şiddetini de içeren çok yönlü bir değerlendirme tercih edilmelidir. Farmakolojik veya nonfarmakolojik yöntemlerin istenmeyen etkileri gözlemlenmelidir. Bireyin yeterince dinlenmesi sağlanmalı ve analjezinin uygulanması için ağrının şiddetlenmesi beklenmemelidir. Hastanın rahatını bozacak ışık ve gürültüden kaçınılması gerekmektedir (39).

Postoperatif Beslenme Yönetimi

Erken Oral Beslenme

SRCHİPEK sonrası gastrointestinal iyileşmenin diğer cerrahi prosedürlere kıyasla daha uzun sürdüğü bilinmektedir. Hastaneye yeniden yatış kabul oranları %11-25 olup yapılan bir çalışmada, ileus ve dehidratasyonun yeniden yatış nedenlerinin üçte birini oluşturduğu saptanmıştır. Buna rağmen, peritonektomi prosedürleri ve HİPEK hastaları da dâhil olmak üzere enteral beslenmenin erken başlatılmasını önermektedir (40).

Kolorektal cerrahi uygulanmış hastalarda postoperatif erken beslenmenin klinik sonuçlara olan etkisini inceleyen retrospektif bir kohort çalışması, açık ve laparoskopik olarak uygulanan cerrahi işlemden sonra erken oral beslenme desteği sağlanan hastalarda sağlanmayanlara göre daha az enfeksiyon, pnömoni, gastrointestinal sistem komplikasyon gelişme insidansının ve yoğun bakım ünitesine kabul oranlarının azaldığı sonucuna ulaşılmıştır (41, 42). Yapılan bir Cochrane incelemesinde, postoperatif 24 saat içinde beslenen hastaların beslenmeyen hastalardan 2 gün önce taburcu olduğu belirlenmiştir (43). Bu sonucu destekleyen bir çalışma ise, hastalardan bir gruba ERAS yaklaşımıyla beslenme desteği uygularken diğer hasta grubuna geleneksel yöntemi uygulamış ve ERAS grubundaki hastaların hastanede kalış süresinin 2,5 gün kısaldığı saptanmıştır (44).

Erken beslenme ile geleneksel beslenmenin klinik sonuçlara olan etkilerinin kıyaslandığı bir Cochrane incelemesinde de erken oral beslenen hasta grubunda barsak motilitesinin daha hızlı sağlandığı, enfeksiyon görülme insidansının daha düşük olduğu ve hasta memnuniyetinin arttığı sonuçlarına ulaşılmıştır (45). Laparoskopik kolorektal rezeksiyon yapılan hastalarda ERAS protokolünün uygulandığı ve uygulanmadığı gruplar karşılaştırılmıştır. Preoperatif dönemde karbonhidrat yüklemesi yapılan ve hem preoperatif dönemde hem de postoperatif dönemde ERAS yaklaşımına uygun olarak beslenen hastalarda kilo kaybının daha az görüldüğü ve hastanede kalış süresinin kısaldığı rapor edilmiştir (46).

- SRCHİPEK uygulanan hastalarda midenin geç boşalması için risk faktörlerin olmaması durumunda (omentektomi), ameliyat gününde berrak sıvılar ve ameliyattan sonra 1.günden itibaren katı gıda alımını içeren erken oral beslenme uygulamasıyla gastrointestinal sistem fonksiyonlarının düzelme süresinde kısalma, mortalite anastomoz sızıntıları ve hastanede kalış süresinin azalması hedeflenir (Orta Kanıt Düzeyi, Güçlü Öneri) (10).

Multidisipliner ekipte yer alan hemşireler, preoperatif ve postoperatif dönemde hastaların nütrisyon durumlarını değerlendirmeli ve ekip ile iş birliğini sürdürerek güncel ve kanıta dayalı yaklaşımlarla uyumlu olacak şekilde beslenme desteği sağlamalıdır (47).

Oral Besin Takviyeleri

Herbert ve ark.'nın (2018) yaptığı Cochrane incelemesinde, erken postoperatif beslenme desteğinin daha kısa hastanede kalış süresi, daha az komplikasyon ve azalmış mortalite ile ilişkili olduğunu belirtmektedir. Ek olarak aynı çalışmada, Cochrane incelemesine dahil ettiği çalışmaların heterojenliği ve daha düşük kanıt kalitesi nedeniyle yorumda dikkatli olunması gerektiğini önermektedir (43). Greco ve ark.'nın (2014) yaptığı meta-analiz çalışmasında, erken oral beslenmenin kolorektal cerrahi uygulamalarında tüm iyileştirilmiş iyileşme programlarının bir bileşeni olduğunu vurgulamaktadır (48). Lau ve ark.'nın (2014) yaptığı randomize kontrol çalışmada, postoperatif ileusun önlenmesinde berrak sıvılardan ziyade düşük rezidülü diyeti desteklemekte ve bu diyetin daha az bulantı, bağırsak fonksiyonunun daha hızlı geri dönmesi

ve daha kısa hastanede kalış süresiyle sonuçlandığını bildirmektedir (49). Oral beslenme takviyeleri randomize kontrollü çalışmalarla desteklenmemekle birlikte, prospektif bir seri, protein açısından zengin takviyelerin bir ERAS programının parçası olarak rol oynayabileceğini önermektedir (50).

- Protein içeriği zengin olan besin takviyelerinin günlük alınan rejime eklenmesi ile gerekli enerji ve protein alımının sağlanması hedeflenir (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).
- Hastanın yeterli besin ve kaloriyi aldığından emin olmak için günlük olarak besin alımı takibi yapılmalıdır (Yüksek Kanıt Düzeyi, Güçlü Öneri) (10).
- SRCHİPEK uygulanan hastalarda yeterli oral alımın sağlanamadığı durumlarda postoperatif 7 gün boyunca enteral beslenme uygulanabilir (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).

Parenteral Beslenme

Gastrointestinal komplikasyonların veya ileusun oral alımı engellediği hastalarda parenteral nütrisyon (PN) düşünülmelidir. En iyi uygulamaların incelendiğinde bir derlemede, 3 günden fazla gecikmenin beklendiği durumlarda erken ek PN'nin tercih edilmesi gerektiğini vurgulamaktadır. (ESPEN kılavuzuna göre 5 gün). SRCHİPEK uygulanan 321 hastadan oluşan retrospektif bir çalışmada postoperatif 1. günde PN'ye başlanmış ve 19 hastada (%6) 5 günden az, 42 hastada (%13) 7 günden az PN ihtiyaç duyulduğu belirtilmektedir (51).

SRCHİPEK uygulanan hastalarda ortaya çıkabilen ileus gibi gastrointestinal sistem komplikasyonları nedeniyle oral alım mümkün olmayabilir. Bu durumda başvurulacak yöntemlerden bir tanesi de parenteral beslenmedir. SRCHİPEK uygulanan 321 hasta ile yapılan retrospektif bir çalışma ile, hastalara postoperatif 1.günde parenteral beslenme yönteminin uygulandığı belirtilmiş olup (52). 19 hastada (%6) 5 günden az, 42 hastada (%13) 7 günden az PN ihtiyacı duyulmuştur (52).

- SRCHİPEK işlemi sonrasında hastalara yeterli oral alım sağlanamadığında ya da az sağlanabildiğinde postoperatif 7 gün boyunca parenteral beslenme uygulanabilir (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).

TPN uygulamasında hastanın yeterli besin ihtiyacının karşılanması için nütrisyon durumunun ve tedaviye yanıtının değerlendirilmesi önerilmektedir. TPN işleminin yol açabileceği metabolik komplikasyonların erken saptanması ve gerekli girişimlerin uygulanabilmesi için elektrolit, kan glikoz düzeyi, asit baz dengesi, vital bulgular ve haftalık kilo takibinin yapılması önemlidir. Ancak beslenmenin değerlendirilmesinde standart olarak albümin ve prealbümin değerlerine bakılmasından kaçınılmalıdır. Çünkü bu parametreler damar geçirgenliğinin artması ve hepatik protein sentezinin değişmesi gibi akut dönem ile ilgili bilgiler vermekte, dolayısıyla beslenme durumunun değerlendirilmesinde yetersiz kalmaktadır. Beslenmenin değerlendirilmesi güvenilir ve geçerli bir risk değerlendirme ölçeği kullanılması gerekmektedir (51).

Postoperatif Glikoz Değerlendirmesi

Kontrolsüz hiperglisemisi olan cerrahi hastaların, normoglisemik hastalara göre daha yüksek mortalite oranına ve daha kötü sonuçlara sahip olduğu bilinmektedir (53). Ayrıca, çok sık uygulanan glikoz kontrol stratejilerine bağlı şiddetli hipoglisemi de artmış mortalite ile ilişkilidir. Bununla birlikte, optimal kan şekeri aralığı tartışmalıdır. Çok sayıda klinik çalışma, kritik hastaların çeşitli popülasyonlarında farklı kan şekeri aralıklarını karşılaştırmıştır, ancak SRCHİPEK için herhangi bir veriye rastlanmamıştır. Perioperatif dönemde kan glukoz düzeyi ile cerrahi alan enfeksiyonlarının ilişkisini inceleyen bir çalışmada; perioperatif glikoz kontrolünün sağlanmasıyla cerrahi alan enfeksiyonu insidansının azaldığı bildirilmiştir. Postoperatif dönemde metabolik stres artışına bağlı gelişebilen hiperglisemi ve insülin direncini önlemek/azaltmak için ERAS yaklaşımına uygun olan girişimlerin uygulanması önemlidir. Preoperatif barsak hazırlığından kaçınılması, hastanın işlem öncesi uzun süre aç bırakılmaması ve postoperatif dönemde erken oral desteğin ve hidrasyonun sağlanması ile barsak fonksiyonlarının kısa sürede normale dönmesinin sağlanması bu girişimlerden bazılarıdır. Hiperglisemi gelişimi ve insülin rezistansını azaltmak için metabolik stresi azaltan ERAS unsurlarının (ameliyat öncesi mekanik barsak hazırlığından kaçınma, cerrahiye 2 saat kalana kadar ameliyat öncesi açlıktan kaçınma, ameliyat sonrası oral alıma erken başlayarak barsak fonksiyonlarının stimülasyonu ve optimal sıvı dengesi) uygulanması önerilmektedir (17).

- SRCHİPEK uygulanmış hastaların kan glikoz

düzeyini 140- 180 mg/dl düzeyinde tutmak için kısa etkili insülinler ya da insülin infüzyonlarının rutin olarak kullanımı önerilmektedir (Düşük Kanıt Düzeyi, Güçlü Öneri) (10).

Kritik hastalarda glisemik kontrolün evrensel olarak kabul edilmiş bir insülin rejimi yoktur. Hedef aralığa ulaşmak ve hipoglisemiden kaçınmak için kan glikoz düzeyi dikkatle izlenmelidir.

Tromboembolinin Önlenmesi

SRCHİPEK uygulanan hastalarda profilaktik bir müdahale uygulanmadığında venöz tromboembolizm (VTE) görülme oranı %30-50 arasındadır (54). Venöz tromboembolinin gelişmesinde öncü olan risk faktörleri arasında peritoneal karsinom indeksi (PCI), kan kaybına bağlı uygulanan kan tranfüzyonu, yapılan ameliyatın kapsamı, süresi ve büyüklüğü, hastanede ve yoğun bakım ünitesinde kalış süresi, hastanede yattığı süreçte ve taburculukta antikoagülanların uygulanma durumudur (17).

Over kanseri tanısı alan hastaların genellikle ileri yaşta ve dolayısıyla daha az mobil olmaları ve uygulanan cerrahi işlem sonucunda lenf nodu diseksiyonun yapılması bu hasta grubunun hemşire tarafından daha dikkatli değerlendirilmesini gerektirmektedir. Hemşireler postoperatif dönemde hastaları tromboemboli yönünden gözlemlemeli, mobilizasyonunu sağlamalı ve antiembolik çorap kullanımları konusunda teşvik etmelidir.

Mekanik Trombofilaksi

Jinekolojik cerrahi işlem uygulanan yüksek riskli hastalar için ise tromboemboli profilaksisinde pnömatik basınç cihazlarının preoperatif dönemde uygulanması ve taburculuğa kadar sürdürülmesi önerilmektedir (55).

Tromboemboli profilaksisinde mekanik profilaksi ile kombine olarak preoperatif ve postoperatif dönemde farmakolojik profilaksi de kullanılabilmektedir. Bunun yanı sıra cerrahi işlemden önce hormon replasman tedavisi ve oral kontraseptif kullanımının sonlandırılması veya yerine başka alternatiflerin kullanılması önerilmektedir (56).

- Hem farmakolojik trombofilaksiye alternatif olarak hem de ikisi birlikte kombine olarak ilk mobilizasyona kadar rutin olarak uygulanmalıdır (Düşük Kanıt Düzeyi, Güçlü Öneri) (10).

Farmakolojik Trombofilaksi

- SRSHİPEK planlanan hastaya işlemden 12 saat önce ve bu hasta grubu riskli olduğu için ameliyattan sonraki 4 hafta boyunca DMAH (düşük molekül ağırlıklı heparin) rutin olarak uygulanmalıdır (Orta Kanıt Düzeyi, Güçlü Öneri) (10).

Uzatılmış Farmakolojik Trombofilaksi

- SRCHİPEK uygulanan hasta hastanede yatarken yapılan trombofilaksinin yanı sıra taburculuk sonrasında yani işlemden sonra 4 haftaya kadar farmakolojik trombofilaksiye devam edilmelidir (Orta Kanıt Düzeyi, Güçlü Öneri) (10).

Erken Mobilizasyon

Uzun süre immobil kalan hastalar pulmoner komplikasyonlar, venöz tromboemboli, insülin direnci gelişimi, kas ve kemiklerde güç kaybı, gastrointestineal sistem fonksiyonlarının normale dönme süresinde uzaması ile erken oral alımın gecikmesi gibi olumsuz durumlarla karşılaşabilmektedir.

SRCHİPEK uygulanan hastaların uzun süre yoğun bakım ünitesinde kalması, ameliyattan sonra yeterli organ perfüzyonunu sağlamak için uygulanan sürekli sıvı tedavisi, intraoperatif dönemde yerleştirilen göğüs ya da abdominal drenler, büyük ve agresif cerrahi sebebiyle ortaya çıkan postoperatif ağrı, uzun süre idrar sondasının kalması gibi nedenlerle erken mobilizasyon engellenebilmektedir. Bu uygulamaların sayılarının azaltılması, uygun rehabilitasyonun sağlanması ve etkili analjezi yöntemi kullanılarak sağlanan ağrı yönetimi ile erken mobilizasyona olanak sağlanabilir (56).

- Hastanın ameliyat günü 2 saat, takip eden günlerde ise taburcu olana kadar günde 6 saat yatak dışında kalması sağlanmalıdır (Düşük Kanıt Düzeyi, Güçlü Öneri) (10).

Hemşireler SRCHİPEK uygulanmış hastaları erken mobilize olmaları konusunda teşvik etmeli ve ilk beslenmelerini yatak dışı örneğin koltuk ya da sandalyede oturarak yemelerini sağlamalıdır. Böylece hastaların erken mobilizasyona uyumu artırılmaktadır.

Ameliyat Sonrası Bulantı ve Kusma

Cerrahi sonrası görülen bulantı ve kusmanın gelişmesinde birçok faktör öncülük etmektedir. Çoğunlukla (vakaların %40-50'sinde) kemoterapik ajanların emetajonik etkisiyle gelişse de HİPEK

işleminde kemoterapik ajanın sistemik alımı sınırlıdır. Arakelian ve ark. 2011 yılında SRCHİPEK uygulanan 76 hasta ile yaptıkları retrospektif bir çalışmada 67 hastada bulantı ve kusmanın görüldüğünü belirtmişlerdir. Ayrıca hastaya uygulanan genel anestezide kullanılan ajanlar da bulantı ve kusma gelişiminde rol almaktadır (17). Farklı etki mekanizmalarına sahip 2 antiemetik ilacın bulantı ve kusmayı önlemede daha etkili olduğu kanıtlanmıştır (57). Ancak bu en iyi iki ajan için spesifik bir ajan kombinasyonu belirtilmemiştir. SRCHİPEK planlanan hastada gelişebilecek olası bulantı kusma riskini en aza indirmek için farklı reseptörleri hedef alan en az 2 antiemetik ajan (ondansetron, deksametazon, droperidol) rutin olarak kullanılmalıdır (Orta Kanıt Düzeyi, Güçlü Öneri) (10).

Hemşireler SRCHİPEK uygulanacak hastalara preoperatif dönemde uygun değerlendirme skalaları kullanarak risk faktörlerini saptamalı ve postoperatif dönemde ortaya çıkan bulantı ve kusmayı yönetmede uygun nonfarmakolojik girişimleri (müzik terapi, hipnoz, akupunktur) bağımsız bir şekilde uygulayabilmelidir. Uygun sıvı tedavisi postoperatif bulantı ve kusma insidansını azaltması açısından önemlidir. Hidrasyonda kullanılacak sıvının kolloid ya da kristaloid olması bulantı ve kusma gelişme riskini etkilememektedir. Hemşireler kanıta dayalı rehberlere uyumlu olacak şekilde hastanın yeterli hidrasyonunu sağlamalıdır (58).

Abdominal ve Torasik Drenler

SRCHİPEK işleminden sonra yaygın olarak görülen solunum komplikasyonları arasında plevral effüzyon, pnömoni, pulmoner emboli ve solunum yetmezliği yer almaktadır. Bu komplikasyonlar nedeniyle hastalar daha uzun süre yoğun bakım ünitesinde kalabilmekte veya tekrar yoğun bakım ünitesine kabul edilebilmektedirler. Preti ve arkadaşlarının yaptıkları bir çalışmada SRCHİPEK işlemi sonrasında %10 pulmoner komplikasyon oranını rapor etmişlerdir. (%4.6 plevral effüzyon + %4.2 si oksijen desteği + entübasyon gerektiren solunum sıkıntısı + %3.2 si pnömoni) (53). Martin ve ark. (2016) yaptıkları bir çalışmada cerrahi sonrası %10,8 plevral effüzyon, iki hastada ise pulmoner emboliyi takiben gelişen ölüm bildirmişlerdir (59).

- SRCHİPEK işleminden sonra profilaktik olarak göğüs drenlerinin yerleştirilmesi ile postoperatif dönemde gelişebilecek pnömotoraks ve plevral effüzyon gibi pulmoner komplikasyonların insidansı azaltılabilir (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).
- SRCHİPEK işleminden sonra yerleştirilen abdominal ve torasik drenler gelişebilecek fistül, yara yeri enfeksiyonu, hastaneden yatış süresi ve mortalite insidansında azalmayı sağlar (Düşük Kanıt Düzeyi, Zayıf Öneri) (10).

Hemşirelerin SRCHİPEK işlemi sonrası yerleştirilen drenlerin takibinde önemli sorumlulukları bulunmaktadır. Hemşireler aldığı çıkardığı takibi yaptığı sırada drenleri boşaltıp hemşire gözlem formuna kaydetmeli ve drenlerin yeniden kurulmasını sağlamalıdır. Drenlerin sebep olabileceği ağrı düzeyi değerlendirilmeli ve uygun farmakolojik ve nonfarmakolojik yöntemler ile hastanın rahatlaması sağlanmalıdır. Aynı zamanda hastaya drenlerin yerini değiştirmemesi, boşaltmaya çalışmaması ve dren hatlarını bozmaması konusunda bilgilendirmeler yapılmalıdır. Torasik drenleri olan hastalar peep kullanımı ve solunum egzersizlerinin uygulanması konusunda teşvik edilmeli ve uygulaması sağlanmalıdır. Drenler hastanın hareket yeteneğini sınırlayabileceği için hastaya destek olunması ve ağrısının olmadığı uygun bir zamanda mobilizasyonunun sağlanması ve sürdürülmesi önemlidir (60).

Sonuç

SRCHİPEK prosedürü, peritoneal karsinomatoz yayılımı olan over kanserli hastalarda da tercih edilmekte olan büyük hacimde hemodinamik ve metabolik değişimlerin ortaya çıktığı riskli bir kombine işlemdir. Literatür incelendiğinde bu yöntemin tercih edildiği hastalarda sadece kemoterapi uygulanan hastalara kıyasla daha yüksek sağ kalım oranlarının görülmesi gibi olumlu yönlerinin olmasının yanı sıra, ameliyat sonrası dönemde birçok komplikasyon ve hastaneye yeniden yatış gibi olumsuz durumlara da yol açabildiği görülmektedir. Bu kapsamda, hastanın fizyolojik homeostazisini sürdürmesine ve yaşam kalitesini artırmasına yardımcı olmada primer sağlık profesyonelleri hemşireler olup bu alanda uzmanlaşan kadın sağlığı ve hastalıkları hemşireleridir. Dolayısıyla kadın sağlığı ve hastalıkları hemşirelerin güncel literatür ışığında ve kanıta dayalı uygulamaları içeren ERAS müdahalelerini de bakım

ve izlem süreçlerine dahil ederek SRCHİPEK işlemi uygulanan hastalarda görülebilecek komplikasyon ve yeniden yatış oranlarını iyileştirebileceği ve hastaların hastaneden daha kısa sürede taburcu olmalarına yardımcı olabilecekleri düşünülmektedir. Bu olumlu sonuçları yükseltmek amacıyla, klinik alanda aktif rol alan kadın sağlığı ve hastalıkları hemşirelerinin, SRCHİPEK prosedürü sonrası hastaya bütüncül bakım vermede ERAS protokolünü ve kanıta dayalı uygulamaları kullanması, klinikte bulunan sağlık ekibine eğitim ve farkındalık seminerleri vermesi, bakım süreçlerini kaydederek kanıt düzeyi yüksek bilimsel çalışmalar yapması veya çalışma gruplarına katılması önerilmektedir.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Geriatric Affective Symptoms in a Case Report: Bipolarity or Dementia?

Bir Olgu Sunumu Eşliğinde Geriatrik Afektif Belirtiler: Bipolarite mi, Demans mı?

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Olgu Sunumu | Case Report
Doi: https://doi.org/10.52827/hititmedj.1494480
Geliş Tarihi | Received: 02.06.2024
Kabul Tarihi | Accepted: 19.10.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Çiçek İE, Meydan M. Geriatric Affective Symptoms in a Case Report: Bipolarity or Dementia? Hitit Medical Journal 2025;7(1):137-142. https://doi.org/10.52827/hititmedj.1494480

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: İEÇ Tasarım: İEÇ Veri Toplama/Veri İşleme: MM, İEÇ Veri Analizi: MM, İEÇ Makalenin Hazırlanması: MM, İEÇ.
Hasta Onamı: Hastanın yasal vasisinden yazılı aydınlatılmış onam ve yayın onamı alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: İEÇ Design: İEÇ Data Collection/Data Processing: MM, İEÇ Data Analysis: MM, İEÇ Manuscript Preparation: MM, İEÇ.
Informed Consent: Written informed consent and consent for publication was obtained from the patient's legal guardian.
Financial Disclosure: There are no financial funds for this article.

Geriatric Affective Symptoms in a Case Report: Bipolarity or Dementia?

ABSTRACT

Bipolar disorder and dementia are two independent and unrelated diagnostic groups. Recently, some commonalities in the pathophysiological processes of bipolar disorder and dementia have been described in the literature. However, this association has not been adequately evaluated at the clinical level, as affective dysregulation in the elderly has typically been attributed to an emotional and behavioral complication secondary to dementia. Here, we present and discuss an 89-year-old male patient who presented to our outpatient clinic with manic symptoms, was not previously diagnosed with bipolar disorder, and was diagnosed with bipolar type VI after clinical evaluation. The manic symptoms began with the addition of antidepressants, while his follow-up and treatment continued with the diagnosis of dementia.

Keywords: Bipolar disorder, dementia, first manic episode.

ÖZET

Bipolar bozukluk ve demans birbirinden bağımsız, ilişkisiz iki tanısal gruptur. Literatürde son zamanlarda bipolar bozuklukların ve demansın patofizyolojik süreçlerinde bazı ortak noktalar tanımlanmıştır. Bununla birlikte, bu ilişki klinik düzeyde yeterince değerlendirilmemiştir, çünkü yaşlılardaki afektif düzensizlik tipik olarak demansa sekonder duygusal ve davranışsal komplikasyona atfedilme eğiliminde olmuştur. Burada; manik semptomatoloji ile polikliniğimize başvuran daha önce bipolar bozukluk tanısı olmayan, demans tanısı ile takip ve tedavisi devam ederken antidepresan eklenmesi ile manik belirtiler başlayan, klinik değerlendirme sonucu bipolar tip VI tanısı ile uyumlu olduğu düşünülen seksen dokuz yaşında erkek hasta ile ilgili klinik bilgiler sunulmuş ve literatür eşliğinde tartışılmıştır.

Anahtar Sözcükler: Bipolar bozukluk, demans, ilk manik epizot.

Introduction

Bipolar disorder is a chronic illness characterized by manic, depressive and mixed episodes and the age of onset is before the age of 50 in a significant proportion of patients. Affective symptoms that appear for the first time in old age are different from the episodes of older bipolar patients and show a different course. These symptoms may occur in the course of dementia or may be precursor symptoms for dementia. In this presentation, we aimed to evaluate a case of manic episode that started after antidepressant treatment in an 89-year-old male patient with dementia. He had no previous diagnosis of bipolar disorder. We discussed the case in the light of the current literature.

Case Report

An eighty-nine-year-old male patient was brought to the outpatient clinic by his relatives because of irritability, insomnia, increased sexual desire, and inappropriate sexual behavior. According to information from his children and medical records, he had been treated for Alzheimer's dementia for about a year and a half. For about four months, he had been experiencing irritability, decreased sleep, increased speech, and preoccupation with marriage and sexuality. For the past week, he had not slept at all at night and had been exhibiting inappropriate sexual speech and behavior. The patient thought his granddaughter was his fiancée and said that they were getting ready to marry soon, that he wanted to buy her an engagement ring, and that she wanted to buy him a gold watch. He had inappropriate sexual conversations with his granddaughter and other women in the family. It was planned to admit the patient to the ward for further investigation and treatment, with the consent of his relatives.

At the time of admission, the patient was taking rivastigmine transdermal patch 9.5 mg/24 hours, memantine 20 mg/day, quetiapine 50 mg/day, and escitalopram 10 mg/day. He had no known systemic disease other than Alzheimer's dementia. A review of his medical records revealed that escitalopram had been added 5 months earlier because of depressive symptoms that had developed during his antidementia treatment, which had been ongoing for 1.5 years. The neurologist, to whom he had been referred with complaints of insomnia and aggressive behaviour, had started him on quetiapine 50 mg/day 1 month earlier.

The patient was born in a village, started working as a carpenter after finishing primary school, and moved to the city with his family before military service. He completed his military service, continued to work as a carpenter, married at the age of 24, had 4 children, had a functional level to support his household, retired voluntarily at the age of 64, started gardening after retirement, and had no psychiatric admissions except for depressive symptoms that appeared at the age of 73.

The history did not describe any prior episodes of mania or hypomania. However, it was noted that he had a lively, active, talkative, and outgoing personality. He had experienced a depressive episode triggered by a stressor at age 74, after his son got into debt. There was a period of insomnia, unhappiness, fear of leaving home, thoughts that he and his family would be harmed, and complaints of auditory hallucinations. He was treated for a short period of time without hospitalization. The patient's relatives did not recall the medications used at that time. The medical records did not contain any information from that time. There was no history of alcohol or drug use. There was no family history of bipolar disorder, major depression or suicide.

On mental status examination, the patient was conscious with partially inadequate orientation to place, time and person. His affect was elevated, with increased speech volume, rapid thought flow, excessive preoccupation with marriage in thought content, disinhibited behavior, decreased sleep and appetite, and impaired judgment and reality testing. The uneducated version of the Mini-Mental State Examination revealed inadequate orientation, attention, and recall, with a score of 15/30.

Vital signs, including temperature, pulse and blood pressure were within normal ranges. Initial laboratory tests, including complete blood count, biochemistry, thyroid function tests, erythrocyte sedimentation rate, C-reactive protein, and urinalysis, were within normal limits. Atrial fibrillation (AF) was detected on electrocardiographic examination, and treatment with enoxaparin 6000 ANTI-XA IU/0.6 mL/day and metoprolol succinate 50 mg/day was started in

consultation with the cardiologist. In diffusion MR examination, acute pathology was not considered because no diffusion restriction was observed but diffuse atrophy and ischemia findings were present.

Because the patient's clinical symptoms were compatible with a manic episode, escitalopram 10 mg was discontinued, and risperidone 0.5 mg was started. Because of persistent sleep disturbances, quetiapine was increased to 100 mg. During clinical follow-up, the patient's mood elevation, sexually inappropriate talk and behavior toward female staff persisted, and risperidone was increased to 1 mg on day 3 of hospitalization and to 2 mg on day 5. No sedation or extrapyramidal symptoms were observed during follow-up. From the third day of follow-up, the patient's sleep duration was found to be adequate and there was no daytime sedation. Beginning on the tenth day, the patient's speech decreased, disinhibited behaviors regressed, sleep duration increased, and the preoccupation with marriage decreased. Toward the end of the second week, when the patient appeared overly subdued, the risperidone dose was reduced to 1 mg and he was discharged for outpatient follow-up and treatment at the family's request. At an outpatient follow-up visit 1 week later, the quetiapine dose was increased to 150 mg because of prolonged sleep latency. No significant side effects were observed with treatment, and the patient's mood was assessed as euthymic. Written informed consent was obtained from the patient's legal guardian before the case was prepared and written.

Discussion

Bipolar disorder is a chronic mood disorder with a prevalence of 1-5% in the population. It has a significant impact on individuals and society due to problems such as impaired occupational and social functioning, increased medical costs, decreased productivity, and increased risk of suicide (1). It typically begins in late adolescence or early adulthood (2).

A diagnosis of mania occurring after the age of 50 in a patient with no history of manic episodes is rare, but clinically significant. Late-onset mania differs from late-onset bipolar disorder and mania in patients diagnosed with bipolar disorder at an older age in several ways, primarily suggesting a more organic etiology. First manic episodes occurring at an older age are often referred to as secondary mania, with cerebrovascular events, medication treatments, metabolic problems, and other neurological disorders often identified as causes in the etiology (3-5). In addition, treatment of the underlying organic cause has been found to contribute to the successful management of the manic episode (5). Although no neurological deficit was found to explain the manic symptomatology in the patient, the presence of previously undiagnosed atrial fibrillation and ischemic lesions on brain imaging suggest vascular dementia. There are studies associating inappropriate sexual behaviors with vascular dementia rather than other dementias (6)

Although the first episode of classic mania is quite rare in the elderly, mood instability, mixed periods of irritability, agitation, and atypical depression may occur in previously healthy individuals beginning in the sixth decade of life, along with cognitive decline. In a review by Akiskal et al, it was suggested that the intersection of dementia and bipolarity could be temporarily defined as "bipolar type VI" (7). In support of this proposal, a case series was published in which 10 elderly patients without a clear history of bipolar disorder but with late-onset affective symptoms, associated behavioral symptoms, and cognitive decline were selected. Clinical features, temperament, cognition, family history, and pharmacological response were assessed to identify prototypical patients to demonstrate the complexity of the dementia-bipolar interface (8). Results showed that mixed and depressive mood symptoms were more common in these patients, most of whom had a premorbid hyperthymic, cyclothymic, and/or irritable temperament, with a psychiatric history and/or family history of mood disorders in most cases. Symptoms were generally resistant to antidepressants and acetylcholinesterase inhibitors, but responded well to mood stabilizers and/or atypical antipsychotics.

Due to the patient's advanced age, history could not be obtained from the patient's peers and parents, resulting in limited history information. Although we did not use a temperament scale due to the patient's age and cognitive status, we believe the premorbid condition is consistent with

characteristics of a hyperthymic temperament based on history and clinical assessment. The patient's hyperthymic temperament may have made it difficult to identify occasional hypomanic episodes, and thus a previous diagnosis of bipolar disorder may have been missed. Although there was no family history of mood disorders, it was understood that the patient had experienced a psychotic depressive episode approximately a decade before the dementia symptoms, and that the manic symptoms were triggered by antidepressant treatment initiated for recurrent depressive symptoms after the dementia diagnosis. The rapid improvement in the patient's symptoms after discontinuation of the antidepressant, initiation of protective antiplatelet therapy for atrial fibrillation, and atypical antipsychotic treatment supports the idea that sexually disinhibited behaviors were related to affective elevation rather than dementia-related behavioral problems.

In addition to neurocognitive symptoms, patients with dementia experience a group of psychological and behavioral symptoms called neuropsychiatric symptoms. These symptoms include apathy, depression, sleep disturbances, hallucinations, delusions, psychosis, agitation, aggression, and disinhibition. (9) Inappropriate sexual talk and behavior, which was prominent in this case, can be considered a symptom of disinhibition, which can be seen in various types of dementia. Symptoms of sexual disinhibition are seen in the early stages of frontotemporal dementia, whereas they occur in the intermediate and advanced stages of Alzheimer's dementia (10). In a recent retrospective study, hypersexual behaviors were found with a frequency of 9.3% in patients with dementia, and male gender, diagnosis of frontotemporal dementia, alcohol, and smoking were reported as factors associated with hypersexual behaviors (11).

Inappropriate sexual behavior in dementia has also been associated with the use of levodopa, benzodiazepines, alcohol and antidepressant treatments. Sometimes undressing and touching the genitals may occur as a result of inability to cope with physical symptoms such as hyperthermia or itching. Or, as in our case, the person with dementia may substitute others as sexual partners because they cannot recognize their relatives. Inappropriate sexual behaviors that occur in old age may lead to the development of feelings such as fear and shame in the caregiver and disruption of the care of the patient with dementia (10).

The fact that inappropriate sexual behaviors and increased sexual desire symptoms were accompanied by symptoms such as elevated mood, increased speech and energy, insomnia and loss of appetite, and met the criteria for mania, led us to move away from the diagnosis of sexual disinhibition that occurs clinically in the course of dementia.

Conclusion

Sometimes late affective symptoms may precede or predict dementia. These symptoms can also be considered a form of pseudodementia. As in our case, affective symptoms may appear after dementia symptoms. Antidepressants may exacerbate behavioral dysregulation and affective symptoms in these patients. Assessing temperament prior to illness and/or a family history of bipolarity and related conditions can provide a broader perspective for understanding these patients. Achieving mood stabilization and avoiding antidepressants in selected patients may provide a better treatment option.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Evaluating Adverse Events and Management Strategies in Foam Sclerotherapy: A Case Report of Sinus Venosus Atrial Septal Defect

Köpük Skleroterapi ile Ortaya Çıkan Sinus Venosus Atrial Septal Defekt: Advers Olaylar ve Yönetim Üzerine Bir Vaka Sunumu

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Vaka Sunumu | Case Report
Doi: https://doi.org/10.52827/hititmedj.1533045
Geliş Tarihi | Received: 14.08.2024
Kabul Tarihi | Accepted: 02.12.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Çiçek İE, Meydan M. Geriatric Affective Symptoms in a Case Report: Bipolarity or Dementia? Hitit Medical Journal 2025;7(1):143-147. https://doi.org/10.52827/hititmedj.1494480

Hakem Değerlendirmesi: Alan editörü tarafından atanan en az iki farklı kurumda çalışan bağımsız hakemler tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: UT Tasarım: UT Veri Toplama/Veri İşleme: UT Veri Analizi: UT Makalenin Hazırlanması: UT, KAT.
Hasta Onamı: Hastadan yazılı aydınlatılmış onam ve yayın onamı alınmıştır.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by independent reviewers working in the at least two different institutions appointed by the field editor.
Ethical Statement: Not applicable
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: UT Design: UT Data Collection/Data Processing: UT Data Analysis: UT Manuscript Preparation: UT, KAT.
Informed Consent: Written informed consent and consent for publication was obtained from the patient.
Financial Disclosure: There are no financial funds for this article.

Evaluating Adverse Events and Management Strategies in Foam Sclerotherapy: A Case Report of Sinus Venosus Atrial Septal Defect

ABSTRACT

Foam sclerotherapy (FS) is widely employed for minimally invasive varicose vein treatment. Despite contraindications in symptomatic right-to-left shunt cases like patent foramen ovale, routine pre-procedure transthoracic echocardiogram (TTE) screening isn't standard. This article discusses managing chest symptoms during FS in a young woman later diagnosed with an unknown sinus venosus atrial septal defect (SV-ASD). FS was administered to a 38-year-old female with symptomatic CEAP-1, who developed sudden shortness of breath and chest tightness. Subsequent diagnosis revealed SV-ASD. Minimally invasive repair followed four weeks later. While FS is generally safe, it poses systemic adverse event risks, emphasizing vigilance in managing SV-ASD patients undergoing FS

Keywords: Adverse events, foam sclerotherapy, sclerotherapy, minimally invasive treatment, sinus venosus atrial septal defect.

ÖZET

Köpük skleroterapi (KS), minimal invaziv varis tedavisi için yaygın olarak kullanılmaktadır. Patent foramen ovale gibi semptomatik sağdan sola şant vakalarında kontrendikasyonlara rağmen, işlem öncesi rutin transtorasik ekokardiyogram (TTE) taraması standart değildir. Bu makale, daha sonra bilinmeyen bir sinus venosus atrial septal defekt (SV-ASD) teşhisi konulan genç bir kadında KS sırasında gelişen göğüs semptomlarının yönetimini ele almaktadır. Semptomatik CEAP-1 tanısı olan 38 yaşındaki bir kadına KS uygulanmış ve hastada göğüs semptomları gelişmiştir. Sonrasında yapılan teşhis SV-ASD'yi ortaya koymuştur. Dört hafta sonra minimal invaziv onarım gerçekleştirilmiştir. KS genellikle güvenli olmakla birlikte, sistemik advers olay riskleri taşır, bu da KS uygulanan SV-ASD hastalarının yönetiminde dikkatli olunması gerektiğini vurgular.

Anahtar Sözcükler: Advers olaylar, köpük skleroterapi, minimal invaziv tedavi, sinus venosus atrial septal defekt, skleroterapi.

Introduction

Sclerotherapy, a procedure widely employed for several years in the minimally invasive treatment of telangiectasias, spider veins, reticular veins, and varicose veins in the lower extremities, is generally regarded as safe (1). Despite its safety profile, sclerotherapy encompasses a spectrum of adverse events (AEs) ranging from simple local reactions to potentially life-threatening complications such as cerebrovascular events, cardiac toxicity, pulmonary embolism, deep vein thrombosis, and severe anaphylactic reactions. Some studies have reported the detection of patent foramen ovale (PFO) in patients who experienced systemic AEs during sclerotherapy. Although systemic AEs are less frequent than local AEs, they can lead to serious outcomes, including fatalities, when they occur (1,2).

This article presents the case of a patient with an undiagnosed sinus venosus atrial septal defect (SV-ASD) who developed chest tightness and shortness of breath likely attributable to air embolism or chemical-induced vasospasm during foam sclerotherapy (FS).

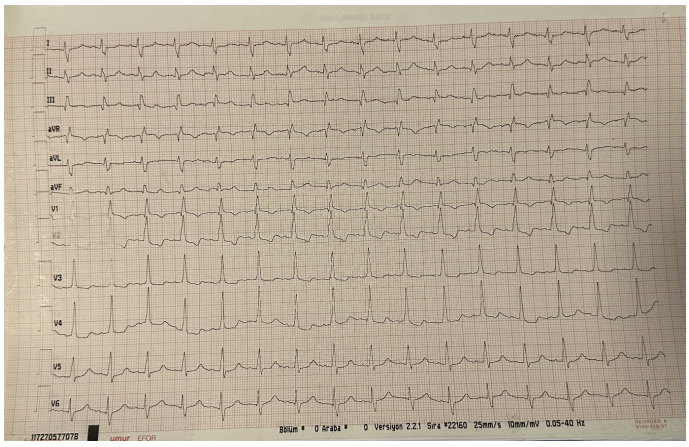
Case Presentation

Informed consent was obtained from the patient for the publication of this case report. A 38-year-old female patient with symptomatic CEAP-1 presented with sudden onset chest tightness and shortness of breath during foam injection sclerotherapy of the reticular vein in her right leg. Pre-procedure Doppler ultrasonography revealed no insufficiency in the great and small saphenous veins, deep venous system, or saphenofemoral junction, with standard diameters. The patient had no known medical history or medications.

Polidocanol foam (1%) (AethoxysklerolVR, Keussler Pharma, Wiesbaden, Germany) was prepared using the Tessari method with a double syringe and a three-way tap (3). After cleansing the target localization with ethyl alcohol, 1 ml of foam was injected into the target vein using a 30G sclerotherapy needle guided by Portable Veinlite (Veinlite LEDXVR, TransLite, LLC, Sugar Land, TX, USA). Compression was applied to the target vein.

While under compression, the patient experienced sudden shortness of breath and chest tightness. She was placed in the Trendelenburg position, and nasal oxygen at 5 L/min was administered. Peripheral vascular access was established, and the patient received 2 ml of pheniramine maleate and 40 mg of methylprednisolone. Enoxaparin 0.6 ml was injected subcutaneously, and 100 mg of acetylsalicylic acid was administered sublingually. Upon examination, her temperature was 37°C, respiratory rate 22 breaths per minute, oxygen saturation 99%, and blood pressure 138/86 mmHg. Electrocardiogram (ECG) showed no evidence of ischemia, with a heart rate of 100 beats per minute and sinus rhythm. Right bundle branch block and 150 degrees right QRS axis deviation were observed on ECG (Figure I). Neurological examination was unremarkable. The patient's symptoms improved after approximately 20 minutes, and further evaluations were conducted. Chest X-ray revealed enlargement of the right side of the mediastinum. Initial high-sensitivity troponin T levels were elevated at 760 ng/L, which decreased to 544 ng/L after 4 hours and 236 ng/L after 24 hours. D-dimer level was 0.48 µg/mL, and all other blood tests were within normal limits. Anaphylaxis due to the sclerosing agent was considered unlikely due to the absence of clinical manifestations. Myocardial infarction was ruled out based on troponin levels and the absence of ischemic findings on ECG. CT pulmonary angiogram for pulmonary embolism yielded negative results.

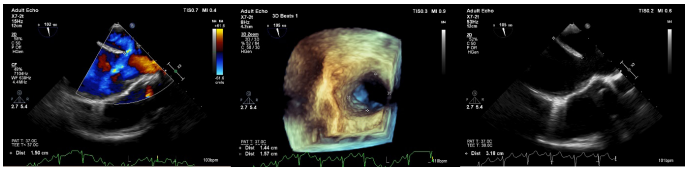
Figure I. ECG recording obtained during onset of patient symptoms.



Transthoracic echocardiogram (TTE) was performed to assess cardiac function and rule out pericardial pathologies. Left ventricular function and heart valves appeared normal, while the right atrium

and ventricle were dilated, and pulmonary artery pressure was within normal range. A left-to-right shunt was identified. After 24 hours of observation, the patient was discharged with enoxaparin 0.6 ml and 81 mg of acetylsalicylic acid.

Figure II. Clinical application of TEE images depicting sinus venosus-atrial septal defect.



Two weeks later, she was readmitted for further evaluation and preparation for atrial septal defect (ASD) surgery. Transesophageal echocardiography (TEE) revealed a left-to-right shunt with a Qp: Qs ratio of 2.1, along with SV-ASD and anomalous right superior pulmonary venous return (Figure II). Coronary artery angiography was not performed due to the absence of risk factors.

Given the patient's cosmetic concerns and young age, a minimally invasive approach was chosen. An incision was made through the fourth right intercostal space, and cardiopulmonary bypass with aortic cross-clamping was utilized with bicaval and femoral artery cannulation. Del Nido cardioplegia induced cardiac arrest under moderate systemic hypothermia.

The interatrial defect was accessed through a right atriotomy extending into the superior vena cava (SVC). Examination within the right atrial cavity revealed SV-ASD near the SVC and the right upper pulmonary vein draining proximally to the SVC. A fresh autologous pericardial patch was sutured with a 5/0 monofilament suture to close the SV-ASD and redirect pulmonary venous flow to the left atrium. SVC expansion plasty was not performed due to the absence of narrowing.

The patient was extubated 4 hours post-surgery and discharged in good condition on the fifth postoperative day with 100 mg of acetylsalicylic acid.

Discussion

Sclerotherapy is designed to induce a controlled thrombophlebitis reaction by inflicting endothelial damage with a sclerosing agent within the vein wall. This process triggers fibrosis and eventual obliteration of the vessel (4). Typically, the liquid sclerosing agent is combined with a gas (such as air or CO2) in a 1:4 ratio using the Tessari method to generate foam, which is then administered to the target vessels through various catheter techniques (3). However, this technique presents drawbacks such as variations in gas/liquid compositions, bubble size, foam behavior, and safety concerns. Systemic AEs may arise due to the pharmacological properties of the sclerosing agent, air embolism, or chemical-induced vasospasm (2).

ASDs represent the third most prevalent congenital heart anomaly in adults, with SV-ASDs accounting for approximately 4-11% of all ASDs. SV-ASD denotes a communication defect between one or more right pulmonary veins and either the superior vena cava (superior sinus venosus) or the inferior vena cava (inferior sinus venosus) (5). While the majority of SV-ASD patients remain asymptomatic throughout childhood, even those with left-to-right shunts may not exhibit discernible symptoms until adulthood. Most SV-ASDs are incidentally detected during evaluations for nonspecific clinical signs such as exertional dyspnea, arrhythmias, and paradoxical embolism.

Paradoxical embolism through ASDs can be triggered by thrombus, fat, or air (6). Several case reports have documented ischemic stroke resulting from paradoxical embolism following foam injection sclerotherapy for varicose veins in patients with PFO. The resulting ischemia may stem from air embolism or chemical-induced vasospasm (7). Moreover, rare yet potentially fatal cardiac complications, including post-sclerotherapy myocardial infarction and sudden cardiac death, have been reported, indicating a similar mechanism of myocardial injury as observed in cerebral events following foam sclerotherapy (8-9). In our case of SV-ASD, the immediate onset of symptoms following foam sclerotherapy suggests myocardial injury due to air embolism or chemically induced vasospasm.

Stroke or cardiac symptoms arising during or after foam sclerotherapy should raise suspicion for ischemia due to paradoxical embolism of the foam through ASDs. It is crucial to acknowledge that such

ischemic events may be attributed to air embolism or chemical spasm (10). While specific screening for the presence of a right-to-left shunt before foam sclerotherapy is not deemed necessary, it is imperative to recognize that foam sclerotherapy represents an absolute contraindication in patients with symptomatic right-to-left shunts (e.g., symptomatic SV-ASD).

As a result, physicians must remain cognizant of the potential serious and even life-threatening AEs associated with sclerotherapy, adequately inform their patients, and be prepared to manage such events effectively. The incidence or prevalence of complications, particularly cardiac AE, is challenging to assess but can be potentially fatal. There is ongoing debate regarding whether all patients should undergo transthoracic echocardiography screening before undergoing sclerotherapy. However, routine TTE screening is not currently feasible.

Future research, leveraging advancing technology, should prioritize the development of sclerosing agents with improved safety profiles. Furthermore, further investigation is warranted to determine the optimal foam volume for safe administration.

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HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Comment on "The Relationship of Gallstone Disease with Serum RBP4 Level, Vitamin D, Lipid Profile, Insulin Resistance and Uric Acid Levels"

"Safra Taşı Hastalığının Serum RBP4 Düzeyi, D Vitamini, Lipid Profili, İnsülin Direnci ve Ürik Asit Düzeyleri ile İlişkisi" Üzerine Yorum

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Editöre Mektup | Letter to Editor
Doi: https://doi.org/10.52827/hititmedj.1520691
Geliş Tarihi | Received: 24.07.2024
Kabul Tarihi | Accepted: 03.10.2024
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Doğantekin B, Çakır Güney B. Comment on "The Relationship of Gallstone Disease with Serum RBP4 Level, Vitamin D, Lipid Profile, Insulin Resistance and Uric Acid Levels". Hitit Medical Journal 2025;7(1):148-150. https://doi.org/10.52827/hititmedj.1520691

Hakem Değerlendirmesi: Editör tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: BD, BÇG Tasarım: BD, BÇG Veri Toplama/Veri İşleme: BD, BÇG Veri Analizi: BD, BÇG Makalenin Hazırlanması: BD, BÇG.
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by editor-in-chief.
Ethical Statement: Not applicable
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: BD, BÇG Design: BD, BÇG Data Collection/Data Processing: BD, BÇG Data Analysis: BD, BÇG Manuscript Preparation: BD, BÇG.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Dear Editor,

We read with great interest the research article titled "The Relationship of Gallstone Disease with Serum RBP4 Level, Vitamin D, Lipid Profile, Insulin Resistance and Uric Acid Levels" by Kurt İnci et al., published in the second issue of Hitit Journal of Science in 2024 (1). We would like to express our gratitude to the authors and the editorial team for their valuable contributions. Through this letter, we aim to highlight specific elements that we believe will enrich the ongoing discussion around the article. Obesity and gallstone disease are frequently co-occurring conditions. Given the rising global prevalence of obesity and metabolic syndrome, investigating the relationship between gallstones and insulin resistance is of significant importance (2). Insulin resistance, as a component of metabolic syndrome, contributes to gallstone disease by altering bile composition and increasing the risk of cholesterol stone formation, alongside other risk factors such as obesity, dyslipidemia, hypertension, and type 2 diabetes. One of the significant objectives of the study conducted by Kurt İnci et al. is to examine the relationship between insulin resistance and RBP-4, a bioactive protein of adipose tissue, and gallstone disease. Given the limited research in this area, we recognize and appreciate the relevance of this study.

However, we wish to express our concerns regarding the exclusion criteria of the study. The Methods section does not specify whether the patients were using medications that could impact the study outcomes, such as metformin, which enhances insulin sensitivity and reduces hepatic glucose production; allopurinol, which decreases uric acid production; or thiazide diuretics, which increase uric acid reabsorption in the kidneys (3-5). The lack of information on whether these medications were used could affect the study's independent variables and outcomes.

The study categorized patients into two groups based on abdominal imaging conducted over the past two years to assess the presence of gallstones. However, there is a potential risk that patients initially classified as stone-free may develop gallstones over nearly a three-year period. A principal limitation of the study is the temporal mismatch between the blood samples collected for RBP-4 evaluation and the ultrasound imaging. This lack of synchronization between imagining, the other retrospectively screened biochemical parameters and blood samples of RBP4 introduces the possibility of variability in the results and constitutes a major limitation of the study.

In conclusion, while recognizing the merit of Kurt İnci's study, we believe that addressing our concerns regarding the exclusion criteria and temporal mismatch will further strengthen the scientific validity and clinical relevance of the findings. We look forward to advancements in this research area with great interest. Furthermore, we wish to express our sincere appreciation to the author, Kurt İnci, for his valuable contribution to the field despite the limited existing literature.

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Response from author:

Dear Editor,

First of all, thank you for your contribution to our article titled 'The Relationship of Gallstone Disease with Serum RBP4 Level, Vitamin D, Lipid Profile, Insulin Resistance and Uric Acid Levels'. The point mentioned by the author that we are based on imaging studies performed within the last 2 years is one of the missing points of the study, but when our patients are evaluated individually, there are only patients with gallstone disease whose imaging studies were obtained in a period of >3 months. The

imaging of the entire patient group without gallstones was within 3 months. Since it was a study derived from a thesis, the details of the study were restricted in the article. However, the fact that this was not stated in the study material method is a deficiency and the author is right in this regard. Patients were not on metformin and did not have a diagnosis of diabetes. The use of allopurinol, which reduces uric acid production, and antihypertensive treatment were questioned and there were no patients using these treatments in our study. I would like to emphasize again that these data were not included in order not to make the article too long since it is a publication derived from a thesis and the author has made very correct points. Thank you very much.
Dr.Bediz Kurt İnci

Response from editor:

The metabolic parameters associated with gallstones have been the focus of numerous studies and remain an area of considerable interest. Kurt İnci et al. evaluated the biochemical parameters linked to gallstone disease, with a primary focus on serum RBP4. Their study did not reveal a statistically significant relationship between gallstones and RBP4, vitamin D, LDL, triglyceride, total cholesterol, uric acid, or HOMA-IR. Conversely, a positive correlation was observed between vitamin D levels and RBP4. This letter addresses potential confounding factors that may affect these relationships, particularly in relation to exclusion criteria and temporal mismatches. Gallstone disease is prevalent and clinically significant. Despite various studies exploring lipid levels, uric acid, and HOMA-IR, the presence of conflicting data underscores the necessity for more comprehensive retrospective or prospective research involving larger patient cohorts. The study conducted by Kurt İnci et al. and the valuable contributions of the authors will provide important insights that will guide the design of future prospective, multicenter, randomized studies.
Dr. Tolga Düzenli

HİTİT MEDICAL JOURNAL
HİTİT ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

e-ISSN: 2687-4717 Cilt|Volume: 7 • Sayı|Issue: 1 - Şubat|February 2025

Comment on "The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy"

"Tiroid Nodül Boyutu ve Özelliklerinin İnce İğne Aspirasyon Biyopsisinin Doğruluğu ve Malignite Riski Üzerine Etkisi" Hakkında Yorumlar

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Makale Bilgisi | Article Information
Makale Türü | Article Type: Editöre Mektup | Letter to Editor
Doi: https://doi.org/10.52827/hititmedj.1589679
Geliş Tarihi | Received: 23.11.2024
Kabul Tarihi | Accepted: 03.01.2025
Yayım Tarihi | Published: 25.02.2025

Atıf | Cite As
Şenoymak, MC. Comments on "The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy". Hitit Medical Journal 2025;7(1):151-153. https://doi.org/10.52827/hititmedj.1589679

Hakem Değerlendirmesi: Editör tarafından değerlendirilmiştir.
Etik Beyanı: Gerek yoktur.
İntihal Kontrolleri: Evet (iThenticate)
Çıkar Çatışması: Yazarlar çalışma ile ilgili çıkar çatışması beyan etmemiştir.
Şikayetler: hmj@hitit.edu.tr
Katkı Beyanı: Fikir/Hipotez: MCŞ Tasarım: MCŞ Veri Toplama/Veri İşleme: MCŞ Veri Analizi: MCŞ Makalenin Hazırlanması: MCŞ.
Hasta Onamı: Gerek yoktur.
Finansal Destek: Bu çalışma ile ilgili herhangi bir finansal kaynaktan yararlanılmamıştır.

Peer Review: Evaluated by editor-in-chief.
Ethical Statement: Not applicable
Plagiarism Check: Yes (iThenticate)
Conflict of Interest: The authors declared that, there are no conflicts of interest.
Complaints: hmj@hitit.edu.tr
Authorship Contribution: Idea/Hypothesis: MCŞ, Design: MCŞ Data Collection/Data Processing: MCŞ Data Analysis: MCŞ Manuscript Preparation: MCŞ.
Informed Consent: Not applicable.
Financial Disclosure: There are no financial funds for this article.

Dear Editor,

I was intrigued by the article by Avcı, titled "The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy," published in Volume 6, Issue 3 of the Hitit Medical Journal in 2024 (1). I express my appreciation to both the author and the editorial team for their insightful contribution. In this letter, I aim to address aspects that may enrich the discussion.

Thyroid nodules affect approximately 50% of individuals (2). Ultrasonographic features and fine-needle aspiration biopsy (FNAB) are vital in malignancy risk assessment and decision-making for surgical interventions. This study, which examines sonographic findings and FNAB results, with particular attention to the differences between large and small nodules, is highly commendable.

However, I wish to comment on the histopathological classification of thyroidectomy specimens used in the article. While the Bethesda system categorizes cytological findings from FNAB into six groups, it is not applied to histopathological evaluations of thyroidectomy specimens. Instead, these are classified as malignant or benign, with additional subcategories (3). The study's use of Bethesda categories for postoperative pathology results, dividing them into three groups, raises some concerns. For instance, the results categorized as Bethesda 4 (group 2) likely represent follicular neoplasms. However, follicular adenomas should be classified as benign, while follicular carcinomas are malignant, based on capsular and vascular invasion. Cases lacking such evaluation are typically noted by pathologists.

Combining Bethesda categories 3 and 4 as an "indeterminate group" for FNAB results is reasonable. However, merging Bethesda 5 ("suspicious for malignancy") and 6 ("malignant") into a single "malignant" category may have impacted the study's outcomes. Bethesda 5 carries a malignancy risk of 67–83%, whereas Bethesda 6 is nearly always malignant (3). The study suggests that FNAB reliability decreases for nodules larger than 27 mm, but this cutoff was derived from a mixed group including Bethesda 5 cases—some of which were benign—and Bethesda 6 cases. This overlap may have influenced the false positive rate and reduced the reliability of the findings. Separate analyses of Bethesda 5 and 6 outcomes would yield more precise conclusions regarding malignancy probabilities.

In conclusion, I commend the authors for their valuable contribution to this critical topic. Their practical conclusions align with current literature, offering insights to guide patient management. I believe my additional points will further enrich the study and foster continued discourse on this important subject.

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Response from Author:

Dear Editor,

I greatly appreciated the letter to the editor regarding my manuscript titled "The Impact of Thyroid Nodule Size and Characteristics on Fine Needle Aspiration Biopsy (FNAB) Accuracy and Malignancy Risk." I extend my sincere gratitude to the author for enriching the discussion with their insightful suggestions, and to you, esteemed editor, for providing me with the opportunity to respond on this matter. The Bethesda system is a well-established method for evaluating cytological findings obtained from FNAB; however, it is not utilized for the histopathological evaluation of thyroidectomy specimens. The author is absolutely correct in pointing this out. Nevertheless, to examine the accuracy of FNAB and derive statistical outcomes, it is essential to ensure that the scoring system at the entry point aligns with the scoring system at the endpoint. For this reason, the postoperative pathology results were grouped to correspond to

the six Bethesda subcategories, with groups defined as follows: Bethesda II for benign lesions, Bethesda IV for indeterminate lesions, and Bethesda VI for malignant lesions. As the author has noted, while the results ideally should be classified as benign or malignant, pathological results can sometimes fall within the indeterminate group. This classification was made solely to maintain the comparability of the data. Regarding the author's suggestion to combine Bethesda V and VI categories, their perspective is undoubtedly valuable and valid. However, based on their rationale, combining Bethesda I and II or Bethesda III and IV would also have been inappropriate. The primary objective of our study was to assess the accuracy of FNAB, and achieving clear distinctions among benign, indeterminate, and malignant results was our main focus. Grouping was necessary to draw reliable conclusions from a relatively small population. Furthermore, as the author rightly mentioned, Bethesda V, classified as "suspicious for malignancy," indicates a malignancy risk exceeding 67%. With malignancy risk exceeding 50%, this category represents a diagnostic threshold that often prompts surgeons, including myself, to opt for total thyroidectomy rather than lobectomy. From this perspective, combining Bethesda V and VI appears logical. In conclusion, I express my gratitude and congratulations to the author for their valuable contributions and recommendations on this significant topic. I also deeply appreciate their kind thoughts about my work. I am confident that future studies with larger populations will further enrich this discussion and help resolve some of the existing uncertainties.

Sincerely,

Dr. Mehmet Alperen AVCI

Response from Editor:

Thank you for your valuable contribution regarding the article titled "The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy" by Avcı et al. Your comments on the methodological challenges of applying the Bethesda classification to postoperative pathology results and its potential impact on the reliability of FNAB findings are highly appreciated. Specifically, your suggestion to analyze Bethesda categories 5 and 6 separately is noteworthy, as it could provide greater clarity in interpreting the results. Furthermore, your emphasis on the reduced sensitivity of FNAB in larger nodules and the importance of a more detailed statistical evaluation of false-positive rates aligns well with current discussions in the literature and offers a valuable perspective to the study. We believe that your constructive critique will serve as a guide for future research in this area. Thank you once again for your insightful contribution, and we wish you continued success in your work.

Sincerely,

Dr. Veysel Barış Turhan