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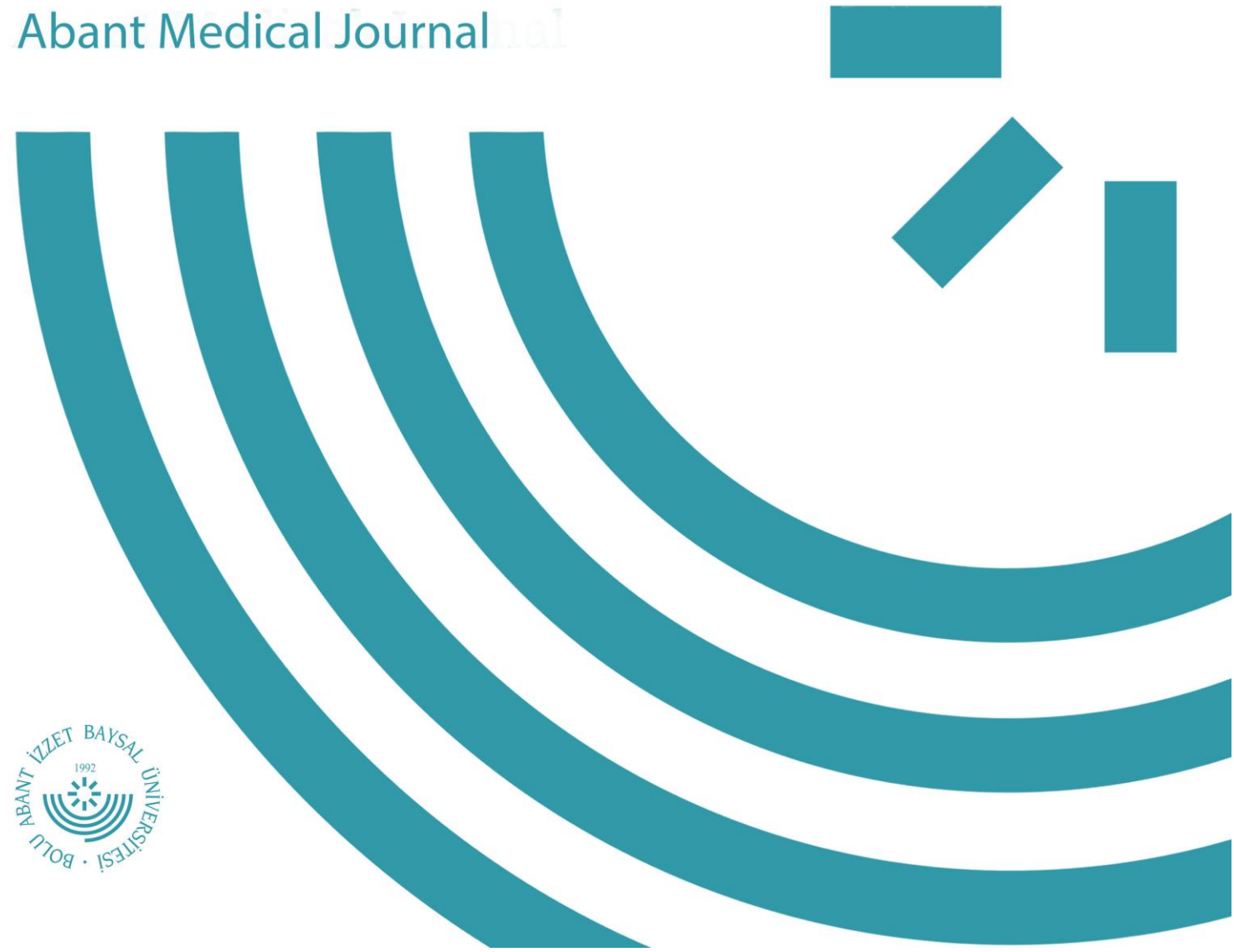

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Abant Tıp Dergisi

Abant Medical Journal

Abant Med J 2024;13(3):98-104, doi:10.47493/abantmedj.1479470

Isolation and Culturing of Primary Neurons from Newborn Mouse Cortex Tissue

Yeni Doğan Farelerden İzole Edilen Korteks Dokusundan Primer Nöron Elde Edilmesi

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Abstract

Objective: This study aimed to establish a reliable protocol for obtaining healthy and long-lived cortical neurons from newborn mice, providing a valuable model for studying neuronal function.

Materials and Methods: Cortical regions of P0 mice were isolated and healthy neurons were obtained by enzymatic and mechanical dissociation. On the seventh day of incubation, the presence of neurons was detected by staining with neuron-specific antibodies. Transgenic mice expressing fluorescent proteins specific to neurons, glia and oligodendrocytes were also used for culture.

Results: Almost all the neurons had adhered to the petri dish bottom by the second hour of incubation. Most of the neurons were healthy and started to grow extension quickly.

Conclusion: Neuron cultures are an important tool in research and are invaluable for studying the behaviour of cells. Nanoparticles facilitate genetic manipulation of these cultures for various biotechnological applications. In particular, they have great potential in areas such as the delivery of genetic material into cells, drug delivery and targeted treatment methods. Such techniques have the potential to open up new avenues for the study and treatment of neurological diseases.

Keywords: Cortex, Newborn Mice, Cell Culture, Neuron Culture, Central Nervous System.

&

Öz

Amaç: Bu çalışma, yeni doğmuş farelerden sağlıklı ve uzun ömürlü kortikal nöronlar elde etmek için güvenilir bir protokol geliştirmeyi ve elde edilen nöronları kullanarak nöron fonksiyonlarını incelemeyi hedeflemiştir.

Gereç ve Yöntemler: P0 farelerin korteks bölgeleri izole edilerek enzimatik ve mekanik ayrıştırma uygulanarak sağlıklı nöronlar elde edildi. İnkübasyonun yedinci gününde nörona özgü antikorlar ile boyama yapılarak nöronların varlığı gösterildi. Ayrıca nöron, glia ve oligodendrositlere özgü floresan proteinleriifade eden transgenik farelerden de kültür yapıldı.

Bulgular: İnkübasyonun ikinci saatinde nöronların neredeyse tamamının kültür kabına yapıştığı gözlemlendi. Elde edilen nöronların büyük kısmının sağlıklı olduğu ve uzantılarının hızlıca büyümeye başladığı gözlemlendi.

Sonuç: Bu protokolü diğer protokollerden ayıran temel özellik, geliştirme sürecini destekleyecek hiçbir faktör veya serum kullanılmamasıdır. Nöron kültürleri, araştırmalarda önemli bir araç olarak kullanılır ve hücrelerin davranışlarını incelemek için oldukça muazzam olanak sağlar. Nanoparçacıklar, bu kültürler üzerinde çeşitli biyoteknolojik uygulamalar için genetik manipülasyonları kolaylaştırır. Özellikle, hücrelere genetik materyal taşıma, ilaç salınımı ve hedeflenmiş tedavi yöntemleri gibi alanlarda büyük potansiyele sahipler. Bu tür teknikler, nörolojik hastalıkların araştırılması ve tedavisi için yeni yollar açabilir.

Anahtar Kelimeler: Korteks, Yenidoğan Fare, Hücre Kültürü, Nöron Kültürü, Merkezi Sinir Sistemi.

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Introduction

Damage to the nervous system often leads to irreversible degenerative processes. Injuries to the central nervous system, in particular, can lead to substantial functional impairments. The primary reason for this is the post-mitotic nature of neurons, which precludes the replacement of lost cells and damaged axonal connections through regenerative mechanisms. Consequently, there are many challenges that still require attention.

In developing treatment strategies for neurological diseases or nervous system trauma, many researchers aim to deepen their understanding of neurodegenerative processes. It would be beneficial for the mammalian central nervous system (CNS) to develop pharmacological interventions that can repair injured or compromised adult tissues (1).

It is important to note that the regeneration mechanism is complex, largely due to the unfortunate reality that regenerative capacity following CNS injuries in mammals is inherently limited (2). The regeneration process involves complex interactions. These include the role of glial cells, scar tissue formed at the site of injury, inflammatory responses and the sensitivity of neurons to growth factors. It is therefore difficult to achieve full recovery from CNS injury. Primary neuron cultures are highly appropriate for investigating the establishment of axonal networks and the molecular mechanisms that underlie cellular maturation in the CNS (3). It might be suggested that primary neuron cultures offer an opportunity to examine several processes, including polarization, neurite outgrowth, axon guidance (pathfinding), synaptogenesis, and neuronal network formation. In addition, it offers the possibility of studying physiological processes that occur in vivo in vitro with more than one neuron at a time (4). This in vitro approach is objective and avoids potential biases that may occur in in vivo settings.

Primary cell cultures, with their homogeneous cell populations, allow to understand normal physiology by simple manipulations (5). Using simple manipulations, it is possible to observe how cells respond to environmental, growth and various chemicals. In addition, these cultures allow us to create disease models, test the effects of drugs and better understand the basic mechanisms of cellular processes. Primary neurons are vulnerable to destruction within a few days, and are capable of producing separate axonal and dendritic structures (6). There are several methods for growing nerve cells. The maturation of neurons can be stimulated by the addition of growth factors (for example, nerve growth factor- NGF). The efficiency of primary neuron cultures heavily depends on the swift and precise dissection, the usage of a appropriate mediums in each step of dissociation, and proper mechanical separation methods to minimize damage (7).

Our laboratory has developed a neuronal culture protocol that ensures reproducibility and promotes rapid and robust axon regeneration. The developed protocol for cell dissociation and plating is both gentle and rapid, allowing for completion in less than two hours. Our short protocol enhances the survival of neurons. Usage of Neurobasal-A increases survival rate and regeneration rate in contrast to many other protocols for cell plating/growth and culture maintenance, respectively. A reliable and reproducible protocol has been established for the preparation of cortical neurons that can be successfully primed from newborn mice.

Materials and Methods

Animals

Newborn mice, including Balb-C and FVB-Tg (Prism)1989Hz/J coded transgenic mice aged between P0 and P3, were used. The animals were maintained in compliance with the ethical and welfare standards established by the Istanbul Medipol Institutional Animal Care and Use Committee (IMU-HADYEK) with the approved reference number [E-38828770-772.02-7790]).

Cell culture

Newborn mice (P0-P3) were euthanized via decapitation and the brain was isolated from the skull. The brain was placed in chilled L-15 medium and mixture of antibiotics and Glutamax were added in proportion as 1% respectively. The cortex was dissected in Hibernate medium under a stereomicroscope. The tissue was then placed in L-15 medium containing 1% papain. It was then incubated at +4°C for 45 minutes. Following incubation, 1% DNase was added and trituration step was carried out. After homogenisation, the tissues were

incubated in a medium containing 10% fetal bovine serum for enzyme inhibition. The homogenized tissues were then centrifuged at 1000rpm for 5 minutes, and the resulting supernatant was discarded. All petri dishes were coated with 1 % poly lysine and incubated for 2 hours at room temperature. The cell pellet was resuspended in Neurobasal Medium supplemented with 1% antibiotics, 1% glutamax and 2% B27, and seeded in each petri dish with a maximum volume of 300 µl. After two hours of waiting for adherence of cells to the petri dish bottom, the growth medium was prepared and the cells were incubated under physiological conditions (37°C, 5% CO2) throughout the experiment (8).

Table 1. Chemicals

Chemicals	Manufacturer
B27	Gibco
Glutamax	Gibco
Antibiyotik	Sigma Aldrich
NBA	Gibco
L15	Sigma Aldrich
Hibernate	Gibco
Poly-L-Lizin	Sigma Aldrich
Fetal Bovine Serum	Sigma Aldrich
Papain	Sigma Aldrich
BSA	Sigma Aldrich
Dnase	Sigma Aldrich
Paraformaldehit	Sigma Aldrich
Triton X-100	Sigma Aldrich
PBS	Sigma Aldrich
Doublecortin	Abcam
Bate III Tubulin	Cell Signaling
Alexa Flour 488 Goat anti chicken	Invitrogen
Alexa Flour 647 Goat anti Mouse	Invitrogen

Immunofluorescence

On the seventh day of the incubation of cells fixation was performed with 4% paraformaldehyde (PFA, Sigma-Aldrich) in PBS at pH 7.4 for 15 minutes at room temperature (RT, 20-22°C). After fixation, cells were washed with PBS, permeabilized with 0.1% Triton X-100 (Sigma-Aldrich) in PBS and washed again with PBS for 5 min. Cells were then blocked with 0.3% w/v BSA in PBS for 30 minutes. Incubation with primary antibodies (Doublecortin Mouse, BetaIII Tubulin Chicken) was performed overnight in a humidified chamber. This was followed by washing steps in PBS and incubation with secondary antibodies Alexa 488 goat anti-chicken and Alexa 647 goat anti-mouse for 1 hour.

The higher magnification images were obtained using a 40x objective in airscan mode of a Zeiss LSM 800 confocal microscope at Istanbul Medipol University SABITA. Sequential scanning was used for image acquisition to reduce crosstalk between different channels. 488 and 647 lasers were used (9).

The study was approved by the Istanbul Medipol University Local Ethics Committee (date: 11.12.2023 and approval number: 68).

Results

The brain tissues were dissected rapidly under sterile and cold conditions. Following two-hour incubation after seeding, it is observed that most of all neurons adhered to the culture dish, and a rapid growth of axonal extensions were seen. The cell culture medium was changed by 50% every three days to remove possible toxicity. The cells were maintained in a serum-free, factor-free environment for an extended period of time (Figure 1).

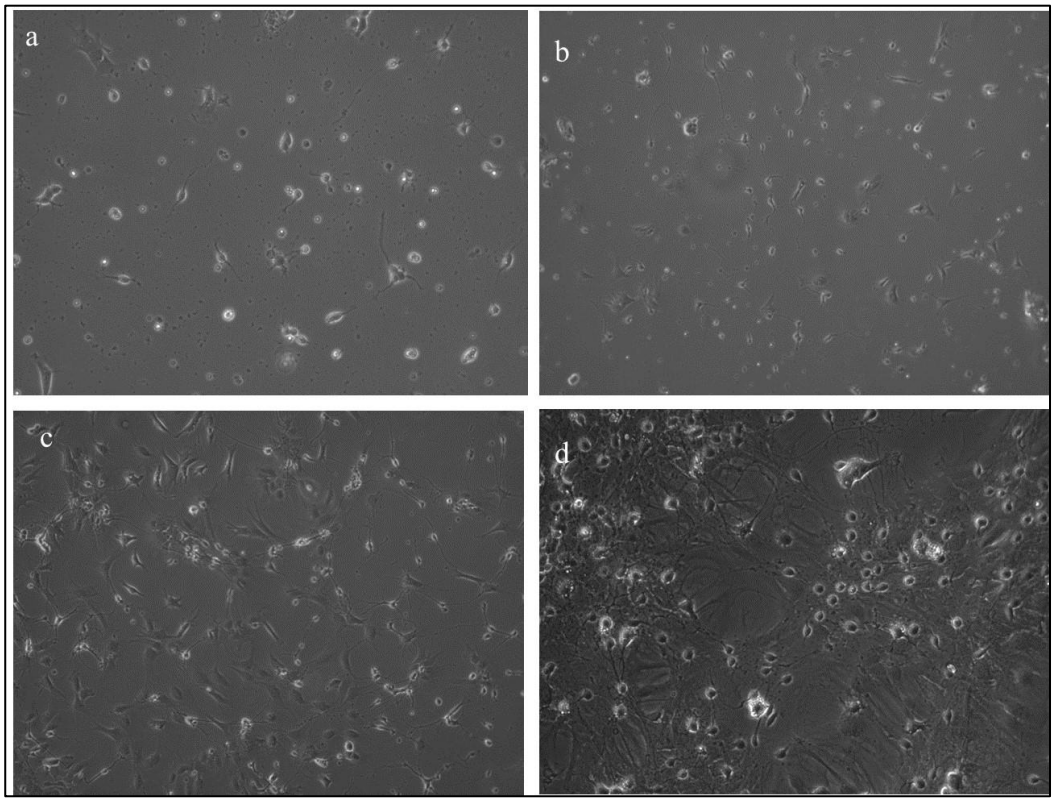

Figure 1. Photographs of the cell culture taken at different times during the incubation period. A: 1st day of cell culture B: 3rd day of cell culture C: 14th day of cell culture D: 21st day of cell culture

Beta-tubulin III, also referred to as Tuj-1, belongs to class III of beta-tubulin protein family, which is one of two structural elements that comprise the cells' microtubule network. While general tubulins participate in a variety of cellular processes, including mitosis and motility, beta-tubulin III specifically found in neurons. Cells stained for beta III tubulin, a neuronal marker, indicated successful axonal elongation (Figure 2).

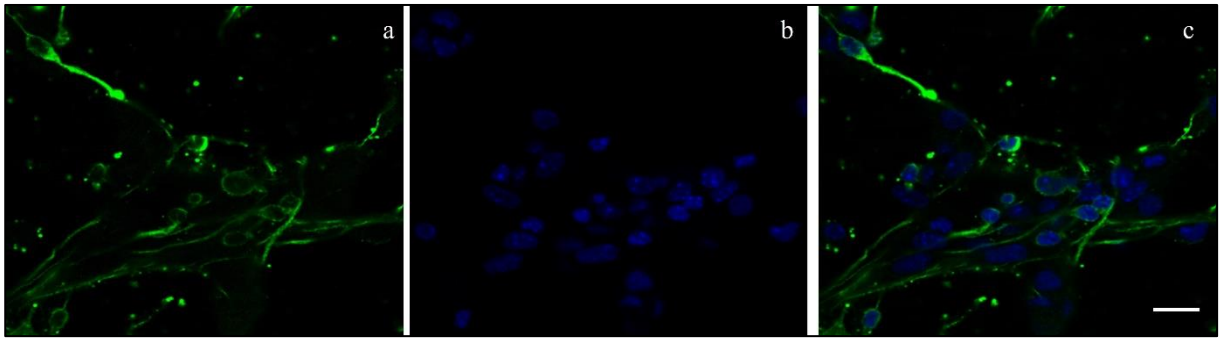

Figure 2. Image of a neuron labelled with Beta III Tubulin. A: shows primary neurons stained for beta III tubulin, a neuronal marker; B: shows a DAPI image; C: shows a merged beta III tubulin and DAPI image (scale bar 100 μm).

Doublecortin (DCX) is a protein that plays an important role in the process of neuronal development and migration. In particular, it has a critical function in the maturation and colonisation of the nerve cells. DCX supports the development of the dendritic structures of neurons and helps to position new neurons correctly in the brain.

DCX is often used as a marker for neural progenitor cells and immature neurons (Figure 3).

The transgenic mice exhibit three distinct fluorophores in specific subsets of brain cells: Mobp regulates Myc-tagged Cerulean (CFP) for blue-green fluorescent oligodendrocytes; Aldh1l1 regulates DsRedMax for red-fluorescent astrocytes; and Snap25 regulates Rpl10a (ribosomal protein L10A) tagged YFP for yellow-fluorescent neurons.YFP expression is primarily localized to the cell body and nucleolus of neurons. The intensity of neuronal YFP fluorescence is notably lower than that of glial fluorescence. Additionally, red fluorescence can be detected through the skulls of newborn pups. Upon exa mination of the distribution of

cortex cells isolated from the transgenic prism animal, it was observed that neurons, astrocytes, and oligodendrocytes were present (Figure 4).

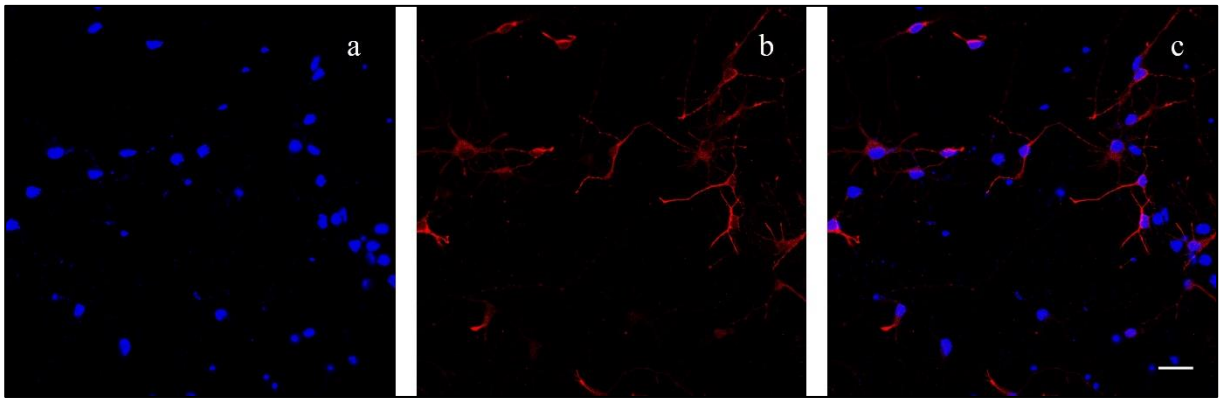

Figure 3. Cellular image showing doublecortin (DCX) immunoreactivity: A: Neurons with DCX immunoreactivity; B: DAPI image; C: Neurons with DCX immunoreactivity and DAPI merge image (scale bar 100 μm).

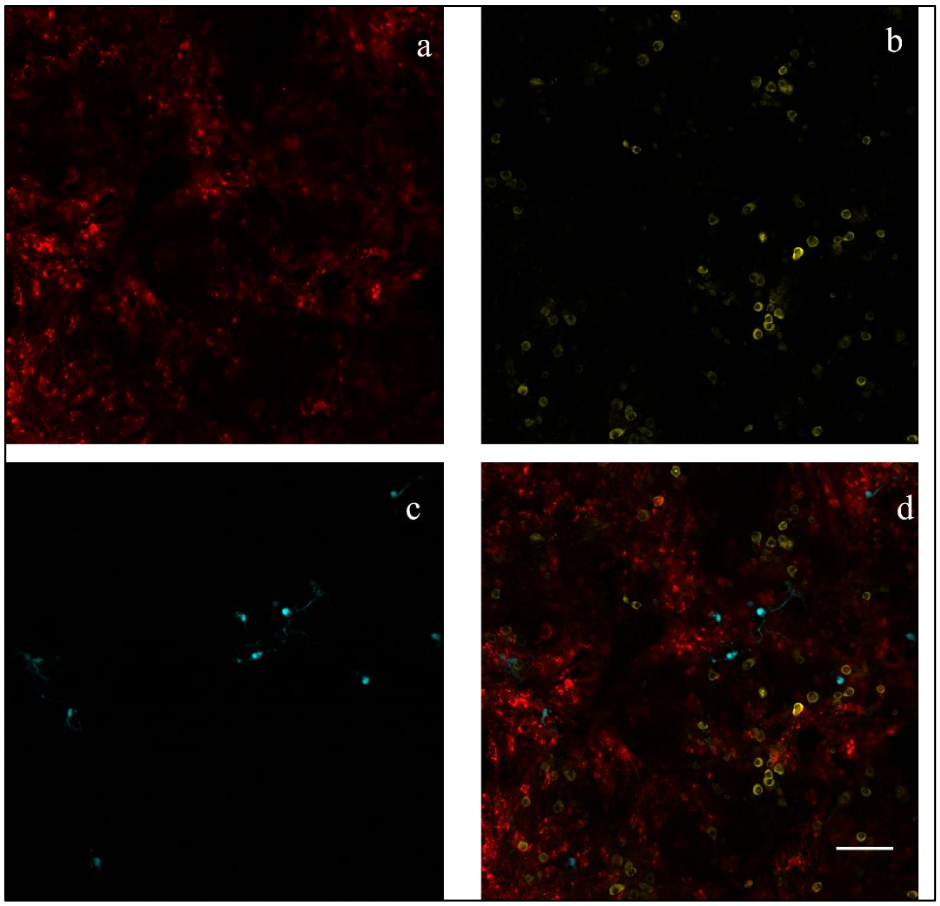

Figure 4. Cells were collected from the cortex of transgenic mice, A:Aldh1l1 controlled DsRedMax, resulting in red-fluorescent astrocytes, B:Snap25 controlled YFP-tagged Rpl10a (ribosomal protein L10A), leading to yellow-fluorescent neurons C :Mobp controlled Myc-tagged Cerulean (CFP) for blue-green fluorescent oligodendrocytes. D: merged image of all cell groups was created (scale bar 100 μm).

Discussion

The postnatal hippocampal culture model represents an appropriate in vitro system for studying neuronal pathophysiology, particularly when transgenic animals are used. The majority of current procedures utilizing

newborn mice are based on protocols originally developed for embryonic culture, which has resulted in inconsistency in culture quality or limitations to P0-P1 pups (10). However, the protocol that we developed enabled us to isolate cortex tissue from animals as young as p10 and transform it into a single cell, maintaining its viability for an extended period and allowing us to observe the rapid regeneration of axons.

Primary neuron cell culture offers a unique framework for investigating neuronal structure and function at a specific level. The protocol currently employed utilizes neuron cultures that are relatively pure, highly reproducible, and contain minimal glial cell contamination. During this process, neurons were maintained in a viable state for several months without the need for additional treatments (such as serum or growth factors).

In contrast to numerous protocols designed for embryonic or postnatal cultures, dissociation of the hippocampus with the protease trypsin has been demonstrated to promote neuronal death. The use of papain, a gentle enzymatic tissue digestion agent, is sufficient to dissociate cells while preserving neuron survival. Similarly, a reduction in mechanical stress can be achieved by minimizing the tirturation procedure, which results in a cell suspension containing a high proportion of viable cells. Furthermore, the survival of neurons was significantly enhanced when the cortex and dissociated cells were maintained in Hibernate medium, a CO_2 independent nutrient medium, throughout the initial stages of the process (11). Papain, an enzyme derived from plants, was used to dissolve the cells. The mechanical separation step is crucial in primary cell culture protocols (12). This step was carried out with great care. The highest amount of living cells were observed.

In neuron cultures, it was observed that during the first week, the number of glial cells was low. This interval served as the perfect time frame to conduct biochemical analyses, including transcriptomic and proteomic assessments, particularly on less contaminated neurons (2). On the other hand it is confirmed that glial cells aid in the maturation and plasticity of neurons through the production of factors (13). So, it is assumed that an increased number of glial cells during the second week has a beneficial impact on neurons in this context. Additionally, secondary cell lines have become a valuable resource for medical research due to their immortal nature.

However, these cell lines have been found to produce variable results over time, likely due to increasing numbers of passages. As a result, the reliability of these cell lines is reduced (14). In contrast, primary cells are genetically more stable and therefore preferred for both pharmacological and biomedical researche (15). They provide prospects for investigation that allow for stricter regulation of cellular functions and processes.

The primary success of CRISPR-Cas9 gene editing has successfully enabled the use of neuronal cultures (16). These cultures also provide demonstrating easy tracking of cellular dynamics through live imaging and electrophysiology (2).

Additionally, another significant benefit is that the technology permits the administration of neurons in drug experiments, thereby reducing the demand for animal testing. With nanoparticles, biotechnological tools designed for various purposes, it is also possible to carry out genetic manipulations in a short time.

Conclusion

The generation of primary mouse cultures followingthe described protocol allows for the undertaking of a multitude of cell biological and biochemical studies. The cultures, prepared with a certain degree of difficulty and care, are highly resilient. These cultures can offer valuable insights into neuronal cellular architecture and function.

The in vitro culture of primary mouse cortical neurons has been successfully established in this study. The viability of these neurons has been demonstrated over an extended period, with no serum or other factors required for their maintenance. The long-term culture of these neurons allows for the examination of their response to DNA damage, apoptosis and other cell death mechanisms.

Ethics Committee Approval: The study was approved by the Istanbul Medipol Institutional Animal Care and Use Committee (IMU-HADYEK) with the approved reference number [E-38828770-772.02-7790]).

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

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References

1. McConnell SK. Plasticity and commitment in the developing cerebral cortex. Prog Brain Res. 1995;105:129-43.
2. Lesuisse C, Martin LJ. Long-term culture of mouse cortical neurons as a model for neuronal development, aging, and death. J Neurobiol. 2002;51(1):9-23.
3. Beaudoin GM 3rd, Lee SH, Singh D, Yuan Y, Ng YG, Reichardt LF, et al. Culturing pyramidal neurons from the early postnatal mouse hippocampus and cortex. Nat Protoc. 2012;7(9):1741-54.
4. Baroncelli L, Lunghi C. Neuroplasticity of the visual cortex: in sickness and in health. Exp Neurol. 2021;335:113515.
5. Lerma J, Morales M, Vicente MA. Single central nervous system neurons in culture. Curr Top Dev Biol. 1998;36:293-302.
6. Ahlemeyer B, Baumgart-Vogt E. Optimized protocols for the simultaneous preparation of primary neuronal cultures of the neocortex, hippocampus and cerebellum from individual newborn (P0.5) C57Bl/6J mice. J Neurosci Methods. 2005;149(2):110–20.
7. Brewer GJ. Isolation and culture of adult rat hippocampal neurons. J Neurosci Methods. 1997;71(2):143-55.
8. Ayşit-Altuncu N, Ulusoy C, Öztürk G, Tüzün E. Effect of LGI1 antibody-positive IgG on hippocampal neuron survival: a preliminary study. Neuroreport. 2018;29(11):932-8.
9. Demir O, Aysit N, Onder Z, Turkel N, Ozturk G, Sharrocks AD, et al. ETS-domain transcription factor Elk-1 mediates neuronal survival: SMN as a potential target. Biochim Biophys Acta. 2011;1812(6):652-62.
10. Moutin E, Hemonnot AL, Seube V, Linck N, Rassendren F, Perroy J, et al. Procedures for Culturing and Genetically Manipulating Murine Hippocampal Postnatal Neurons. Front Synaptic Neurosci. 2020;12:19.
11. Viesselmann C, Ballweg J, Lumbard D, Dent EW. Nucleofection and primary culture of embryonic mouse hippocampal and cortical neurons. J Vis Exp. 2011;(47):2373
12. Hu CY, Du RL, Xiao QX, Geng MJ. Differences between cultured cortical neurons by trypsin and papain digestion. Ibrain. 2022;8(1):93-9.
13. Sammoura FM, Popova D, Morris A, Hart RP, Richardson JR. Methods for shipping live primary cortical and hippocampal neuron cultures from postnatal mice. Curr Res Neurobiol. 2022;4:100069.
14. Aras MA, Hartnett KA, Aizenman E. Assessment of cell viability in primary neuronal cultures. Curr Protoc Neurosci. 2008;Chapter 7:Unit 7.18.
15. Eroglu C, Barres BA. Regulation of synaptic connectivity by glia. Nature. 2010;468(7321):223-31.
16. Sandoval A Jr, Elahi H, Ploski JE. Genetically Engineering the Nervous System with CRISPR-Cas. eNeuro. 2020;7(2):ENEURO.0419-19.2020.

Abant Tıp Dergisi

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Evaluation of Demographic and Clinical Characteristics of Patients Diagnosed with Herpes Zoster

Herpes Zoster Tanılı Hastaların Demografik ve Klinik Özelliklerinin Değerlendirilmesi

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Abstract

Objective: Varicella-zoster virus (VZV) infections result in two distinct clinical entities: varicella (chickenpox) and herpes zoster (HZ). VZV, the causative agent of chickenpox, remains latent in the dorsal root or cranial nerve ganglia and reactivates due to suppression of the cellular immune system, leading to HZ. Risk factors for HZ include advanced age, stress, concomitant infections, use of immunosuppressive drugs, and comorbid conditions.

This study retrospectively evaluates patients diagnosed with HZ who presented to our hospital. The aim is to determine the frequency of herpes zoster based on age, gender, season, and months, as well as the accompanying diseases, complications, and treatments provided.

Materials and Methods: Patients diagnosed with HZ (ICD10 code B02) who presented to our hospital's dermatology outpatient clinic between December 1, 2022, and November 30, 2023, were included in this study using our hospital's automation system.

Results: A total of 211 patients were included in the study, consisting of 115 women (54.50%) and 96 men (45.50%), with a female/male ratio of 1.19. The average age of the patients diagnosed with HZ was found to be 53.38 years. It was observed that HZ occurred more frequently in march (12.32%), august (11.37%), and april (9.95%), and seasonally, it was more common in the spring (29.86%). The most commonly affected body region was the trunk (54.5%), and the most frequently involved dermatome was thoracic (46.4%). The most common comorbidities in patients diagnosed with HZ were hypertension (32.05%) and diabetes mellitus (12.82%). The most frequently administered treatment was valacyclovir (47.87%). Postherpetic neuralgia (PHN) was observed in 37 patients (17.53%) with HZ.

Conclusion: As the frequency of HZ increases with age, early recognition and treatment are crucial for reducing pain, viral spread, and complications. There is a need for large-scale studies on the clinical and demographic data of HZ.

Keywords: Varicella, Herpes, Zoster.

&

Öz

Amaç: Varicella-zoster virus (VZV) enfeksiyonları varisella (suçiçeği) ve herpes zoster (HZ) olarak bilinen iki farklı klinik tabloya neden olur. Suçiçeği etkeni olan VZV dorsal kök veya kranial sinir gangliyonlarında latent halde kalır ve hücresel immün sistemin baskılanması sonucu reaktive olur ve HZ'ye yol açar. İleri yaş, stres, eşlik eden enfeksiyonlar, immunsupresif ilaç kullanımı, ek hastalıklar zona için risk faktörleri olarak sayılabilir.

Bu çalışmada hastanemize başvuran HZ'si olan hastalar retrospektif olarak değerlendirilmiştir. Herpes zosterin yaş, cinsiyet, mevsim ve aylara göre görülme sıklığının, eşlik eden hastalıkların, komplikasyonların ve verilen tedavilerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya, 1 Aralık 2022 ile 30 Kasım 2023 tarihleri arasında hastanemiz dermatoloji polikliniğine başvuran ve HZ tanısı konulan (ICD10 B02 kodlu) hastalar, hastane otomasyon sistemi kullanılarak dahil edilmiştir.

Bulgular: Çalışmaya 211 hasta dahil edilmiştir. 115'i kadın (%54,50), 96'sı erkek (%45,50) olup kadın/erkek oranı 1,19 olarak saptanmıştır. HZ tanılı hastaların yaş ortalaması 53,38 olarak bulunmuştur. HZ'nin mart (%12,32), ağustos (%11,37) ve nisan (%9,95) ayında, mevsim olarak ise ilkbaharda (%29,86) daha sık görüldüğü saptanmıştır. Hastalığın en fazla tuttuğu vücut bölgesinin gövde (%54,5); en fazla tutuğu dermatomun torakal (%46,4) olduğu görülmüştür. HZ tanılı hastalarda en fazla görülen hastalıklar hipertansiyon (%32,05) ve diabetes mellitus (%12,82) olarak bulunmuştur. Hastalara en sık verilen tedavinin valasiklovir (%47,87) olduğu saptanmıştır. HZ hastalarının 37'sinde (%17,53) postherpetik nevralji (PHN) görüldüğü saptanmıştır.

Sonuç: Yaş ilerledikçe sıklığı artan HZ'nin erken tanınması ve tedavisi ağrıyı, viral yayılımı ve komplikasyonları azaltması açısından önem taşımaktadır. HZ'nin klinik ve demografik verileri açısından geniş çaplı çalışmalara ihtiyaç olduğu gözlenmektedir.

Anahtar Kelimeler: Su Çiçeği, Uçuk, Zona.

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Introduction

Varicella-zoster virus (VZV) is a member of the Herpesviridae family, causing two distinct clinical entities known as varicella (chickenpox) and herpes zoster (shingles) (1).

Following primary infection (varicella), VZV becomes latent in nerve tissue. VZV has been identified in dorsal root ganglia, cranial nerve ganglia, various autonomic ganglia, and astroglia in the enteric nervous system (1). During reactivation, VZV replicates in neuron cell bodies. Subsequently, virus particles spread from the cell bodies to the nerve, reaching the dermatome corresponding to the affected nerve. In the affected dermatome, the virus causes inflammation and vesicle formation. Pain associated with VZV is due to the inflammation of the affected nerves (1,2).

The disease typically presents unilaterally, with grouped vesicles on an erythematous base in one or more dermatomes. Patients may present with symptoms such as pain, burning, stabbing, or itching. Early initiation of treatment within the first 72 hours in shingles patients, who may present not only to dermatology clinics but also to primary healthcare services, reduces pain, viral spread, and complications. In mild herpes zoster (HZ) cases, local wound care is sufficient. Systemic treatments include acyclovir, valacyclovir, famciclovir, and brivudin (1,3,4).

The most common complication following shingles is postherpetic neuralgia (PHN). PHN is defined as pain and altered sensory perception persisting for at least three months in the area affected by shingles and has an incidence rate ranging from 9% to 34% (5,6).

This study aims to determine the clinical and demographic characteristics, accompanying diseases, the affected dermatome, presenting symptoms, the month and season of hospital presentation, treatments provided, and the occurrence of PHN in patients with herpes zoster presenting to our hospital.

Materials and Methods

Patients diagnosed with HZ (ICD10 code B02) who presented to our hospital's dermatology outpatient clinic between December 1, 2022, and November 30, 2023, were included in this study using our hospital's automation system. The medical records of patients diagnosed with HZ were reviewed, and data on age, gender, presenting complaint, involved dermatome(s), affected body region, month and season of presentation, treatments administered, comorbid conditions, and the presence of postherpetic neuralgia (PHN) were recorded. All data were divided into categorical and numerical variables. Categorical data were described using count and percentage, while numerical data were described using the mean. Microsoft Excel was used for statistical analysis.

The study was approved by the Bolu Abant İzzet Baysal Unıversıty Clinical Researches Ethics Committee Approval (date: 05.12.2023 and approval number: 2023/413).

Results

A total of 211 patients were included in our study, with 115 females (54.50%) and 96 males (45.50%), resulting in a female-to-male ratio of 1.19. The average age of the patients was 53.38 years, with an average age of 54.47 years for female patients and 52.29 years for male patients. Of these patients, 12 were in the pediatric age group (<18 years), 79 were in the geriatric age group (>65 years), and the remaining 120 patients were between 18 and 65 years old. Pain was the presenting complaint in 152 patients (72%), burning in 33 patients (16%), and itching in 26 patients (12%) (Figure 1). The most frequent season of presentation was spring (63 patients, 29.86%), and the least frequent season was autumn (45 patients, 21.33%) (Figure 2). The months with the highest number of cases were March (26 patients, 12.32%), August (24 patients, 11.37%), and April (21 patients, 9.95%). The most commonly affected dermatome was thoracic (98 patients, 46.4%), followed by cervical (69 patients, 32.2%), and lumbosacral (46 patients, 21.3%) (Figure 3). The affected body regions included the trunk (115 patients, 54.5%), head and neck (50 patients, 23.69%), and extremities (42 patients, 19.9%), with genital involvement in 3 patients and disseminated involvement in 1 patient. Forty-nine different comorbid conditions were found in the patients included in the study. The most common comorbid conditions were hypertension (HT) in 50 patients (32.05%) and diabetes mellitus (DM) in 20 patients (12.82%). Malignancies

were identified in 8 patients (5.12%), including ocular malignant neoplasm, leukemia, pancreatic cancer, thymoma, colon cancer, breast cancer, stomach cancer, and lung cancer. The most commonly administered systemic treatment agent was valacyclovir (101 patients, 47.87%), followed by brivudin (66 patients, 31.28%), acyclovir (38 patients, 18.01%), and topical treatment agents (6 patients, 2.84%) (Figure 4). PHN developed in 37 patients (17.53%), with PHN observed in 17.39% (20 patients) of female patients and 17.71% (17 patients) of male patients. Among the patients diagnosed with PHN, 13 had no comorbid conditions, while hypertension was the most common comorbidity in 13 patients. One patient with PHN had pancreatic cancer.

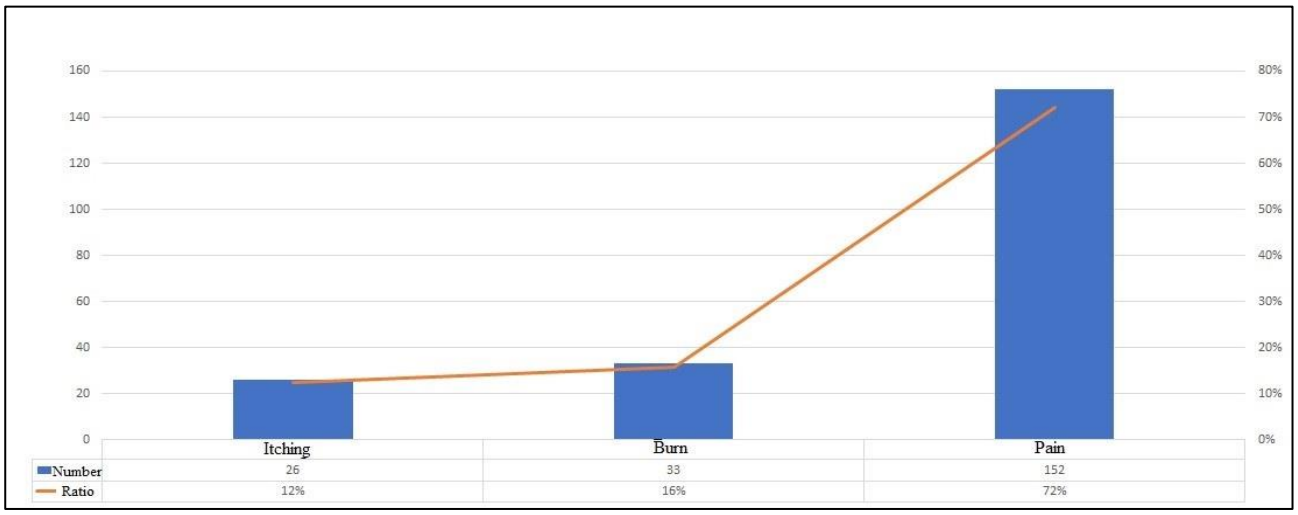

Figure 1. Complaints of patients with herpes zoster.

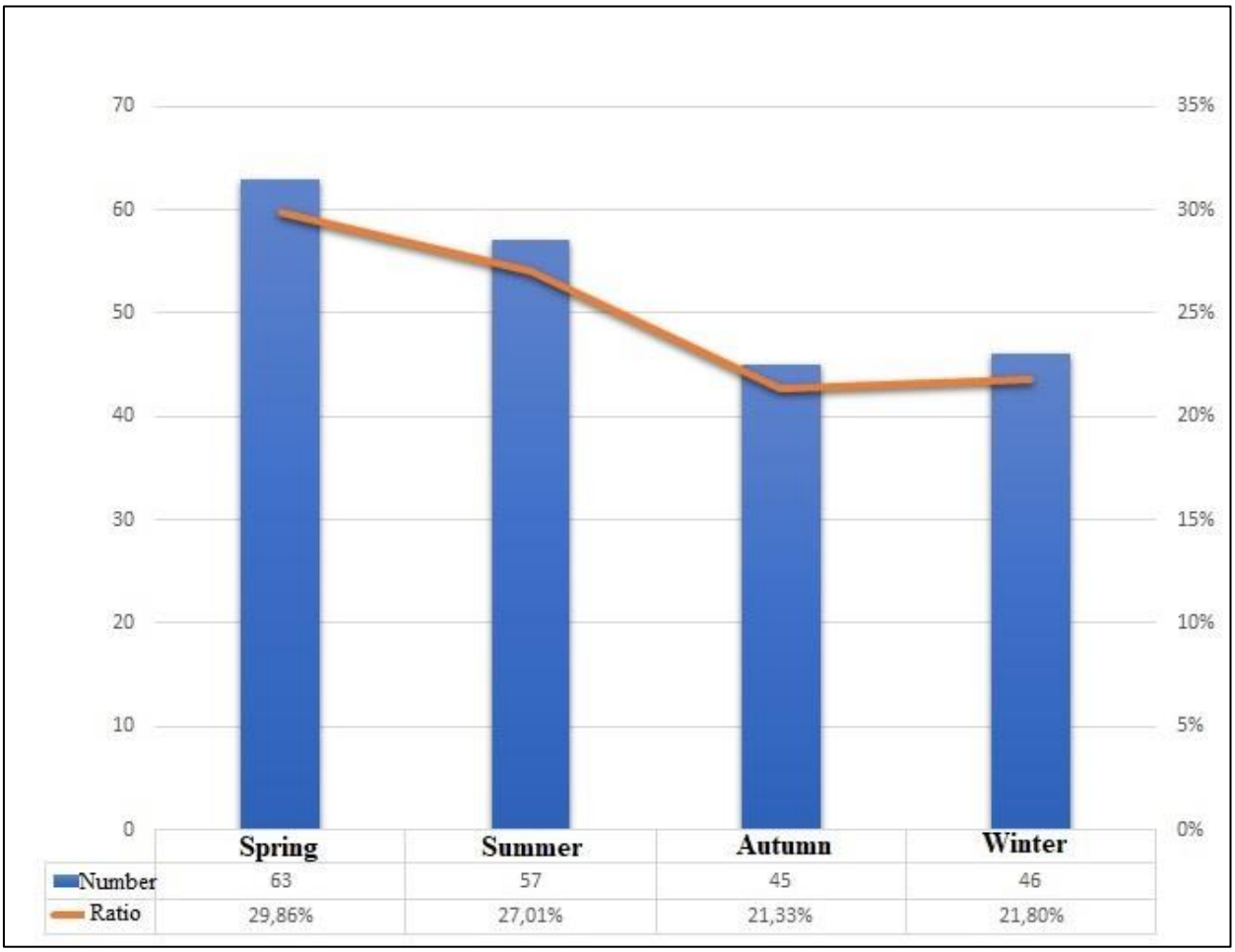

Figure 2. The seasonal distribution of patients with herpes zoster.

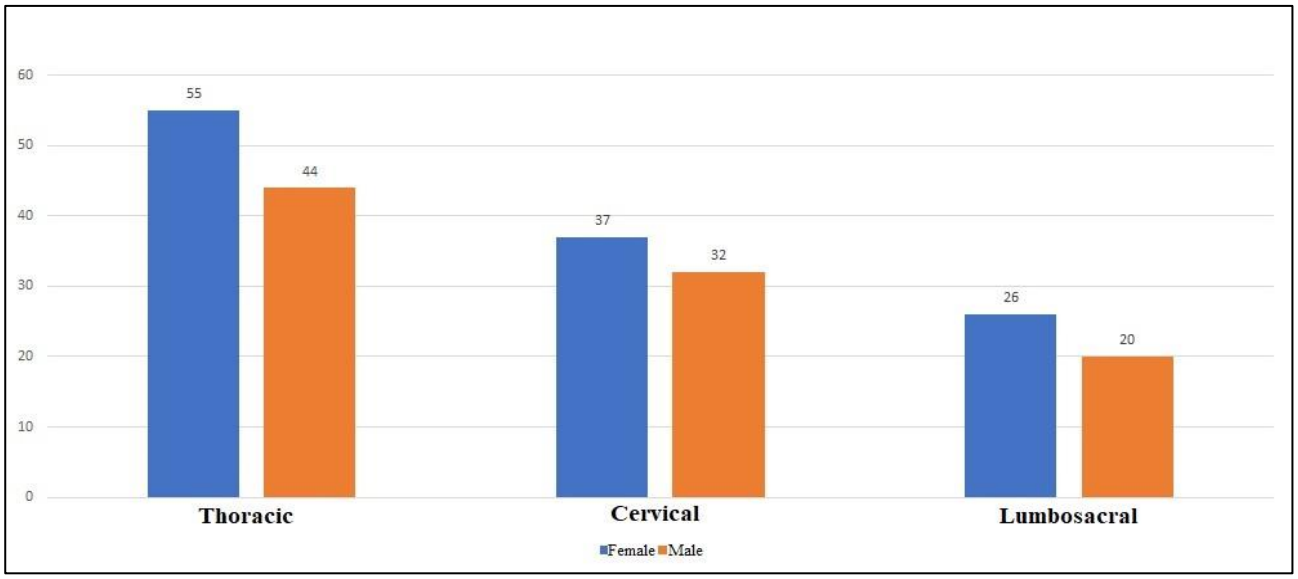

Figure 3. The distribution of patients with herpes zoster by dermatome and gender

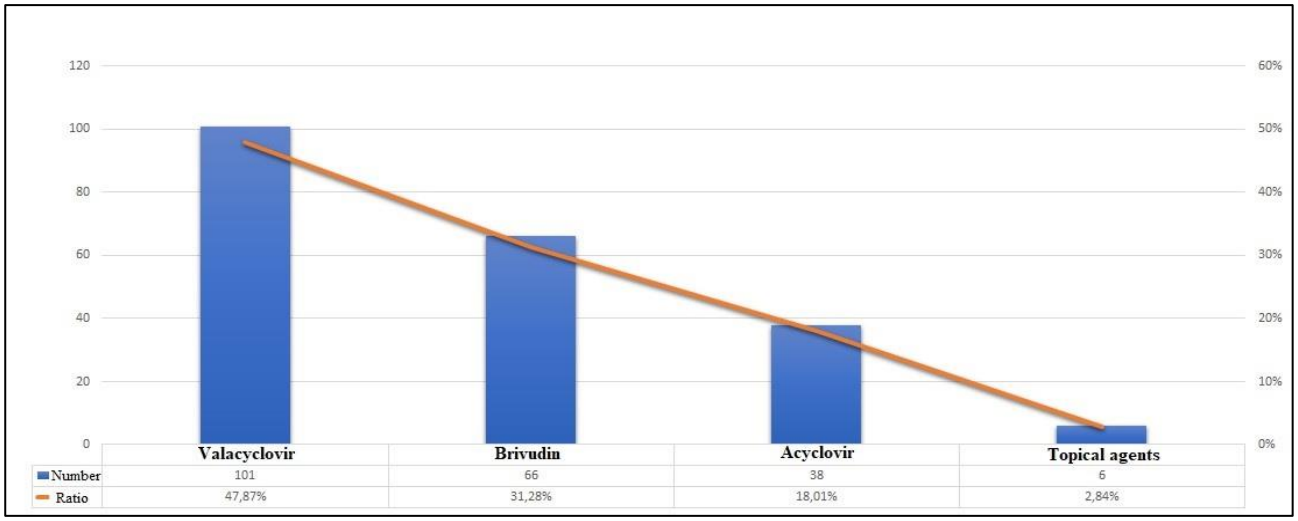

Figure 4. The number and rates of treatments given to patients with herpes zoster.

Discussion

The lifetime risk of developing shingles ranges between 10-20%. The annual incidence of shingles is estimated to be 1.5-3 per 1000 persons (2,3). A study by Van Oorschot et al. reported incidence rates of 6.6–9.03 per 1000 for North America, 5.23–10.9 per 1000 for Europe, and 10.9 per 1000 for the Asia-Pacific region (7).

Studies examining the demographic characteristics of HZ patients show variability in the female-to-male ratio. A meta-analysis by Zhang et al. and studies conducted in our country found a higher number of female patients, similar to our study (2,8,9,10). However, some studies have reported a higher incidence in male patients (5). These differences may be explained by the time period of the study, the number of patients included, and the differences in the immune system between males and females.

While HZ can occur at any age, its frequency increases with age, likely due to the decline in immunity with aging (1). The frequency of HZ is lower in children and young adults and may be associated with metabolic and neoplastic diseases (1). A study conducted in our country reported that 72.1% of shingles patients were over the age of 40 (11). In our study, the disease was most frequently observed in the 18-64 age group (56.9%), with an incidence rate of 5.6% in the pediatric age group and 37.5% in the geriatric age group. No comorbid conditions were detected in the pediatric age group.

Risk factors for HZ include being over the age of 50, immunosuppression, infections, and stress (4). The disease is also seen in healthy individuals (5). Acer et al. reported that at least one systemic disease accompanied herpes zoster in 54.8% of patients, with hypertension, diabetes mellitus, and coronary artery disease being the most common comorbidities (8). Similarly, Küçükçakır et al. identified hypertension and diabetes mellitus as the most frequent systemic diseases accompanying herpes zoster in their study (11). In our study, hypertension and diabetes mellitus were the most common comorbid conditions associated with herpes zoster. Malignancy was identified in 8 patients with HZ. Conversely, 110 patients (52.1%) had no systemic diseases accompanying herpes zoster.

Studies investigating the relationship between the disease and seasons or months, and the seasonal variations in the frequency and characteristics of HZ, are limited. It has been suggested that ultraviolet radiation during summer months may trigger VZV reactivation (12). Seasonal variations in HZ frequency may also be related to seasonal differences in immune system function (5,12). Berlinberg et al. reported that the frequency of HZ was higher in the summer (12). While some studies reported the opposite, there are also studies indicating no seasonal differences (5,8). In our study, HZ frequency increased in the spring and summer, particularly in March, August, and April. Larger series of cases are needed to elucidate seasonal and monthly differences.

HZ is frequently characterized by rashes that do not cross the midline of the trunk (13). In our study, the most common involvement was in the trunk and thoracic dermatomes, followed by cervical involvement. Similar findings were reported in studies conducted in our country, where thoracic dermatome involvement was commonly observed (8,10,11).

Pain is usually the first symptom in patients due to inflammation of the affected nerve in herpes zoster. As in our study, Etgü's study also identified pain as the most common symptom (2). In the study, pain was followed by complaints of itching and burning in HZ patients.

The standard treatment for HZ includes acyclovir, valacyclovir, and brivudin. If there is resistance to acyclovir, famciclovir can be used as an alternative (1). In our study, the most commonly administered treatment agent was valacyclovir, followed by brivudin. Similarly, Acer et al. found valacyclovir to be the most frequently chosen treatment agent (8).

Shingles is typically a self-limiting disease that resolves within 7-10 days with or without treatment. However, it can cause severe complications in some patients (1,5). Postherpetic neuralgia (PHN) is the most common complication associated with herpes zoster. Early initiation of treatment is crucial for pain control and prevention of PHN (1). The incidence of PHN increases with age. Advanced age, widespread rash, severe pain, and immunocompromised status are factors that may increase the likelihood of PHN (14). Alicino et al. reported that PHN incidence increases with age (15). Studies conducted in our country have reported PHN development rates of 27.7%, 4.7%, and 21.75% (8,10,11). In our study, PHN was detected in 17.53% (37 patients). The most common comorbid conditions in patients diagnosed with PHN were hypertension, asthma, and diabetes. The average age of patients who developed PHN was ... years. One patient with PHN had a malignancy.

Conclusion

In conclusion, there are few studies on the clinical and demographic characteristics of herpes zoster in our country. Our study presents the clinical and epidemiological features of HZ cases in the Bolu region. Given that our data cover a limited time period, more extensive studies are needed to investigate the clinical and demographic characteristics of HZ.

Ethics Committee Approval: The study was approved by the Bolu Abant Izzet Baysal University Clinical Researches Ethics Committee Approval (date: 05.12.2023 and approval number: 2023/413).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

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References

1. Patil A, Goldust M, Wollina U. Herpes Zoster. A Review of Clinical Manifestations and Management. Viruses. 2022;14(2):192.
2. Etgü F. Herpes Zoster tanısıyla takıp edilen hastaların demografik ve klinik özelliklerinin değerlendirilmesi. Ege Tıp Dergisi. 2023;62(3):449-56.
3. Guzman-Holst A, Cervantes-Apolinar MY, Favila JCT, Huerta-Garcia G. Epidemiology of Herpes Zoster in Adults in Mexico: A Retrospective Database Analysis. Infect Dis Ther. 2023;12(1):131-41.
4. Dai YX, Yeh FY, Shen YJ, Tai YH, Huang N, Chang YT, et al. Cigarette smoking and risk of herpes zoster: a population-based cohort study in Taiwan. Clin Exp Dermatol. 2021;46(7):1293-8.
5. Hayran Y, Akpınar Ü, Yalçın B. Herpes Zoster Tanısıyla Takip Edilen Hastaların Demografik, Klinik ve Laboratuvar Özelliklerinin Değerlendirilmesi. Ankara Eğitim ve Araştırma Hastanesi Tıp Dergisi. 2020;53(Ek Sayı 1):33-40.
6. Rosamilia LL. Herpes Zoster Presentation, Management, and Prevention: A Modern Case Based Review. Am J Clin Dermatol. 2020;21(1):97-107.
7. van Oorschot D, Vroling H, Bunge E, Diaz-Decaro J, Curran D, Yawn B. A systematic literature review of herpes zoster incidence worldwide. Hum Vaccin Immunother. 2021;17(6):1714-32.
8. Acer E, Erdoğan HK, Bulur I, Acar EM. Evaluation of demographic and clinical characteristics of 166 patients with herpes zoster in the Kırşehir region. Turkderm. 2018;52(3):95-9.
9. Zhang Z, Liu X, Suo L, Zhao D, Pan J, Lu L. The incidence of herpes zoster in China: A meta-analysis and evidence quality assessment. Hum Vaccin Immunother. 2023;19(2):2228169.
10. Demirci Saadet E, Hasanbeyzade S. Evaluation of the Demographic and Clinical Characteristics of Patients Diagnosed with Herpes Zoster. Genel Tıp Derg. 2023;33(2):148-153.
11. Küçükçakır O, Aliağaoğlu C, Turan H, Yanık M, Gürlevik Z, Acer E, et al: Retrospective evaluation of patients with herpes zoster followed up in our department between 1999- 2010. Turkderm 2012;46(4):186-90.
12. Berlinberg EJ, Kim E, Deiner MS, Patterson C, Porco TC, Acharya NR. Seasonality of herpes zoster and herpes zoster ophthalmicus. J Clin Virol. 2020;126:104306.
13. Kelley A. Herpes zoster: A primary care approach to diagnosis and treatment. JAAPA. 2022;35(12):13-8.
14. Johnson RW, Alvarez-Pasquin MJ, Bijl M, Franco E, Gaillat J, Clara JG, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. Ther Adv Vaccines. 2015;3(4):109-20.
15. Alicino C, Trucchi C, Paganino C, Barberis I, Boccalini S, Martinelli D, et al: Incidence of herpes zoster and postherpetic neuralgia in Italy: Results from a 3-years population-based study. Hum Vaccin Immunother 2017;13(2):399-404.

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Impact of Adenotonsillectomy on Pediatric Blood Profiles

Adenotonsillektominin Pediatrik Kan Profilleri Üzerindeki Etkisi

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Abstract

Objective: Adenotonsillar hypertrophy (ATH) is a common condition in children, often leading to obstructive sleep apnea and other complications. This study aimed to evaluate the impact of adenotonsillectomy on various blood parameters in children with ATH.

Materials and Methods: Medical records of 84 children diagnosed with ATH and/or chronic tonsillitis, who underwent adenotonsillectomy, were reviewed. Key parameters analyzed included white blood cell count (WBC), platelet count (PLT), hemoglobin (Hgb) levels, mean platelet volume (MPV), and platelet distribution width (PDW). Blood samples were collected preoperatively, and at postoperative day 1, week 1, and month 3, and results were compared.

Results: A significant decrease in MPV, PDW, and Hgb levels was observed immediately postoperatively. Interestingly, Hgb levels significantly increased three months post-surgery, returning to or surpassing preoperative levels. Although platelet counts remained unchanged, the temporary reduction in RBC count, Hgb, and Hct levels suggests a physiological response to surgical blood loss and trauma. These parameters normalized within three months, reflecting the body's effective compensatory mechanisms.

Conclusion: Adenotonsillectomy significantly impacts certain blood parameters in the short term, with most values normalizing by the three-month follow-up. These findings emphasize the importance of monitoring hematologic changes postoperatively and suggest that adenotonsillectomy, while causing temporary alterations in blood parameters, is ultimately a safe and effective procedure for managing ATH in children.

Keywords: Adenotonsillectomy, Hemoglobin, Adenotonsillar Hypertrophy, Platelet, Tonsillectomy.

&

Öz

Amaç: Adenotonsiller hipertrofi (ATH), çocuklarda sık görülen bir durumdur ve sıklıkla obstrüktif uyku apnesi ve diğer komplikasyonlara yol açar. Bu çalışmanın amacı, ATH'li çocuklarda adenotonsillektominin çeşitli kan parametreleri üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntemler: ATH ve/veya kronik tonsillit tanısı konulan ve adenotonsillektomi geçiren 84 çocuğun tıbbi kayıtları incelendi. Analiz edilen temel parametreler arasında beyaz kan hücresi sayısı (WBC), trombosit sayısı (PLT), hemoglobin (Hgb) seviyeleri, ortalama trombosit hacmi (MPV) ve trombosit dağılım genişliği (PDW) yer aldı. Kan örnekleri ameliyattan önce ve ameliyattan sonraki 1. gün, 1. hafta ve 3. ayda toplandı ve sonuçlar karşılaştırıldı.

Bulgular: MPV, PDW ve Hgb seviyelerinde ameliyattan hemen sonra önemli bir azalma gözlendi. İlginç bir şekilde, Hgb seviyeleri ameliyattan üç ay sonra önemli ölçüde artarak ameliyat öncesi seviyelere geri döndü veya onları geçti. Trombosit sayıları değişmeden kalsa da RBC sayısı, Hgb ve Hct düzeylerindeki geçici azalma, cerrahi kan kaybına ve travmaya karşı fizyolojik bir tepki olduğunu düşündürmektedir. Bu parametreler, vücudun etkili telafi edici mekanizmalarını yansıtarak üç ay içinde normale dönmüştür.

Sonuç: Adenotonsillektomi, kısa vadede belirli kan parametrelerini önemli ölçüde etkiler ve çoğu değer üç aylık takipte normale döner. Bu bulgular, hematolojik değişikliklerin ameliyattan sonra izlenmesinin önemini vurgulamaktadır ve adenotonsillektominin, kan parametrelerinde geçici değişikliklere neden olsa da çocuklarda ATH'yi yönetmek için nihayetinde güvenli ve etkili bir prosedür olduğunu düşündürmektedir.

Anahtar Kelimeler: Adenotonsillektomi, Hemoglobin, Platelet, Adenotonsiller Hipertrofi, Tonsillektomi.

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Introduction

The palatine tonsils are dense, compact clusters of lymphoid tissue found in the side wall of the oropharynx, bordered at the front by the palatoglossus muscle and at the back by the palatopharyngeus and superior constrictor muscles (1). The adenoids, another essential part of the immune system, are situated on the roof and back wall of the nasopharynx (2). Together, the tonsils and adenoids are components of Waldeyer's ring, a circle of lymphoid tissue in the pharynx that is vital for protecting the body from pathogens. The size of the tonsils changes with age, individual variations, and health conditions, usually growing quickly around the fifth or sixth year of life and reaching their largest size during puberty.

Assessing the tonsils and adenoids should begin with a thorough medical history, as this can reveal symptoms indicative of adenotonsillar hypertrophy (ATH). Symptoms of ATH encompass feeding difficulties in young children, mouth breathing, noisy breathing, loud snoring, frequent night awakenings, excessive daytime drowsiness, bedwetting, night terrors, behavioral shifts, and poor school performance. A physical exam might show adenoid facies, marked by a dull facial look, flattened nasolabial folds, an open mouth, and protruding upper teeth. In severe cases, heart failure might occur, and children may sleep in unusual positions, like the sniffing position or with an extended neck. Growth can be impacted, leading to failure to thrive.

Adenotonsillar hypertrophy is the leading cause of upper airway blockage in children, resulting in various short-term and long-term symptoms. Short-term issues include mouth breathing, nasal blockage, nasal-sounding speech, snoring, obstructive sleep apnea (OSA), chronic sinus infections, and repeated ear infections. Long-term complications of OSA involve growth delays, heart problems, and cognitive issues like low IQ, learning and behavior difficulties, hyperactivity, and poor focus (3). The primary indications for adenotonsillectomy in children are recurrent adenotonsillitis, repeated episodes of serous otitis media, peritonsillar abscess, and, most commonly, apnea associated with adenotonsillar hypertrophy (4). Despite improvements in surgical techniques, postoperative hemorrhage continues to be a frequent cause of mortality and morbidity in patients after tonsillectomy (5). Post-tonsillectomy hemorrhage is rare, yet it remains the leading cause of reoperation and mortality in children following tonsillectomy (6).

Given the significant health impact of ATH, understanding the systemic effects of adenotonsillectomy is essential. Platelet indices and white blood cell (WBC) count are key indicators of systemic inflammation and overall health (7). This study aims to investigate the changes in blood markers in patients with ATH who underwent adenotonsillectomy, providing insight into the broader physiological effects of this common surgical intervention.

Materials and Methods

This study was conducted at the Van Education and Research Hospital Otorhinolaryngology Department and reviewed retrospectively. Data from patients treated between 2016 and 2018 were utilized. Ethical approval was obtained from the Van Education and Research Hospital Clinical Research Ethics Committee, with decision number 2016/4. The study included 84 children (44 male, 40 female) who underwent adenotonsillectomy using the cold knife dissection method for tonsillectomy and the curettage method for adenoidectomy. Exclusion criteria included systemic disease or intraoperative bleeding exceeding 200 cc. All participants were residents of Van with at least an average socioeconomic status. The outcome parameters assessed included mean values of WBC, hemoglobin (Hgb), hematocrit (Hct), platelet distribution width (PDW), and mean platelet volume (MPV), measured preoperatively, on postoperative day 1, at one week postoperatively, and at three months postoperatively. Data was reviewed retrospectively, and postoperative values were compared to preoperative values. Statistical analysis was performed using SPSS® 20.0 software (SPSS Inc., Chicago, IL, USA). Variables such as WBC, Hgb, Hct, PDW, and MPV were analyzed using repeated measures ANOVA. The McNemar test was used to compare postoperative values with preoperative values. A p-value of <0.05 was considered statistically significant.

Results

The study population consisted of 44 male children (52.3%) and 40 female children (47.6%), with a mean age of 7.07 ± 0.27 years (range: 3 to 10 years). The mean values of WBC, Hgb, Hct, PLT, PDW, and MPV were

recorded at four different times: before the operation, on the first day after the operation, one week after the operation, and three months after the operation. (Table 1). Compared to preoperative values, Hgb, MPV, and PDW significantly decreased ($p < 0.05$) on postoperative day 1 and week 1. WBC values significantly increased on postoperative day 1 ($p < 0.05$). There was no significant difference in preoperative versus postoperative PLT counts. No post-tonsillectomy bleeding was observed in any patient. By three months post-surgery, blood levels had returned to or surpassed preoperative values, with significant increases in Hgb, Hct, MPV, and PDW ($p < 0.05$).

Table 1.
WBC, Hgb, Htc, PLT, PDW, MPW values of participants

	WBC	Hgb	Htc	PLT	PDW	MPV
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Median (min-max)	Mean±SD
Preop	7.7±2.9	12.27±0.86	36.81±2.32	299000±70000	16.3 (15.5–18.7)	8.32 ±1.12
Postop 1.day	8.4±3.1	12.08±0.85	36.24±3.54	295000±72000	15.4 (13.9–16.8)	8.07 ±1.08
Postop 1.week	7.8±2.8	12.37±0.83	37.13±2.82	298000±75000	15.6 (14.0-17.5)	8.10±1.05
Postop 3.month	7.5±2.5	12.71±0.85	38.13±3.60	300000±71000	16.0 (15.2-18.6)	8.21±1.20

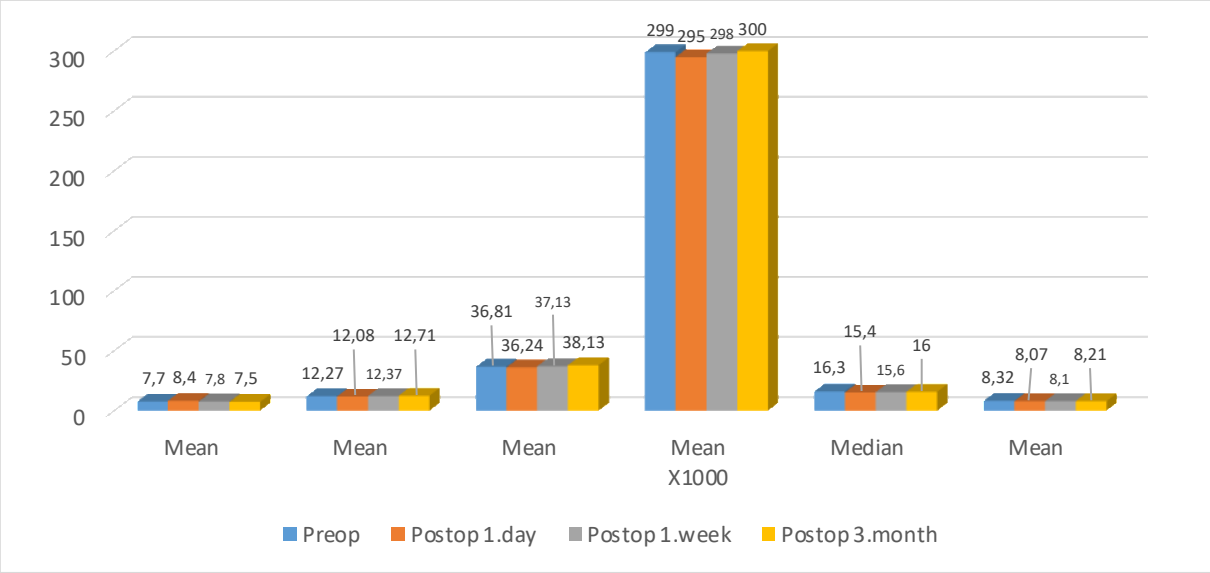

Figure 1. WBC, Hgb, Htc, PLT, PDW, MPW values of participants.

Discussion

Tonsillar hypertrophy is now the most common reason for tonsillectomy in children. Tonsillar hypertrophy is often accompanied by adenoid hypertrophy.

Adenotonsillar hypertrophy (ATH) is closely linked to sleep-disordered breathing (SDB) in children (8). Hypertrophic tonsils causing acute upper airway obstruction are typically associated with acute infections rather than chronic ones (9). Chronic tonsillar hypertrophy can be asymptomatic but may cause significant enlargement, which is responsible for up to 80% of obstructive sleep apnea (OSA) cases in children. Severe cases of OSA can result in cor pulmonale, pulmonary hypertension, pneumonia, chronic hypercapnia or hypoxia, and ultimately, right ventricular heart failure (10). Adenotonsillectomy is a common treatment for

ATH and is highly effective for treating upper airway obstruction and recurrent tonsillitis, regardless of the technique used. Consequently, tonsillectomy, with or without adenoidectomy, is among the most frequently performed surgeries in pediatric ENT practice (4). Perioperative blood loss is an unavoidable aspect of surgery, and minimizing intraoperative blood loss is ideal. Perioperative and postoperative blood loss in adenotonsillectomy is influenced by the surgical technique, the patient's coagulation status, perioperative infections, and systemic metabolic conditions (11).

In children, blood loss and postoperative effects are more pronounced compared to adults. Children's physiological mechanisms are less adaptable to rapid blood loss, making them more susceptible to significant changes in blood parameters and complications (12). The early postoperative period involves the body's compensation for blood loss.

The study's results provide valuable insights into these physiological responses. The study's results suggest that adenotonsillectomy is effective for ATH, with an immediate decrease in MPV, PDW, and Hgb levels reflecting a physiological response to surgical trauma and blood loss. The transient reduction in RBC count, Hgb, and Hct levels aligns with similar studies documenting decreases in these parameters following surgical interventions in children (11-13).

Importantly, these blood parameters normalized within three months post-surgery, indicating effective compensatory mechanisms and recovery. During this period, increases in hematopoietic and other growth factors contribute to overall body growth and accelerated hematopoiesis. A study by Gumussoy reported significant increases in growth factors and hormones (14). The observed increases in RBC, Hb, Hct, MPV, and PDW at one and three months postoperatively can be attributed to these growth factors. This supports previous research showing that, despite initial decreases, blood values typically return to baseline levels as healing progresses (12).

The stable platelet count suggests that while surgery affects some blood parameters, the overall platelet count remains unaffected, minimizing significant bleeding risks. The study emphasizes that perioperative and postoperative blood loss is influenced by surgical technique, coagulation status, and systemic conditions. Minimizing intraoperative blood loss is crucial to optimizing outcomes and reducing complications, aligning with best practices in pediatric ENT surgery (4).

The findings highlight the particular vulnerability of children to blood loss and postoperative effects. Children's less adaptable physiological mechanisms compared to adults underscore the need for careful monitoring and management during the perioperative period to ensure optimal recovery and mitigate risks.

Despite providing valuable insights, the study's retrospective design and use of a single surgical technique may limit generalizability. Future research could benefit from prospective studies comparing different surgical techniques and their impact on blood parameters and overall recovery.

Conclusion

Adenotonsillectomy remains a highly effective procedure for managing ATH and associated complications. The findings emphasize the importance of monitoring blood parameters and addressing postoperative issues promptly. Further research is needed to refine surgical techniques, minimize blood loss, and enhance recovery strategies for pediatric patients undergoing adenotonsillectomy.

Ethics Committee Approval: The study was approved by the Van Education and Research Hospital Clinical Research Ethics Committee, (approval number: 2016/4).

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References

1. Kenna MA, Amin A. Anatomy and physiology of the oral cavity. In: Snow JB, Wackym PA, editors. Ballenger's Otorhinolaryngology Head and Neck Surgery. 17th ed. Shelton (CT): BC Decker Inc.; 2009. p. 769–74.
2. Susan S, Harold E, Jermiah CH, David J, Andrew W. Pharynx. In: Susan S, editor. Gray's Anatomy: The Anatomical Basis of Clinical Practice. 39th ed. Philadelphia (PA): Elsevier; 2005. p. 619–31.
3. Scadding G. Non-surgical treatment of adenoidal hypertrophy: the role of treating IgE-mediated inflammation. Pediatr Allergy Immunol. 2010;21(8):1095–106.
4. Kontorinis G, Schwab B. Significance of advanced hemostasis investigation in recurrent, severe post-tonsillectomy bleeding. J Laryngol Otol. 2011;125(9):952–7.
5. Liu L, Rodman C, Worobetz NE, Johnson J, Elmaraghy C, Chiang T. Topical biomaterials to prevent post-tonsillectomy hemorrhage. J Otolaryngol Head Neck Surg. 2019 Sep 6;48(1):45.
6. Lee AC, Haché M. Pediatric anesthesia management for post-tonsillectomy bleed: current status and future directions. Int J Gen Med. 2022 Jan 4;15:63–9.
7. Akelma AZ, Mete E, Cizmeci MN, Karaarslan U, Sert S. The role of mean platelet volume as an inflammatory marker in children with chronic spontaneous urticaria. Allergol Immunopathol (Madr). 2015;43(1):10–3.
8. Feng X, Li G, Qu Z, Liu L, Näsström K, Shi XQ. Comparative analysis of upper airway volume with lateral cephalograms and cone-beam computed tomography. Am J Orthod Dentofac Orthop. 2015;147(2):197–204.
9. Brodsky L. Adenotonsillar disease in children. In: Bluestone CD, Stool SE, Kenna MA, editors. Pediatric Otolaryngology. 2nd ed. Philadelphia (PA): W.B. Saunders Company; 1996. p. 15–39.
10. Richardson MA. Sore throat, tonsillitis, and adenoiditis. Med Clin North Am. 1999;83(1):75–83.
11. Alatas N, San I, Cengiz M, Iynen I, Yetkin A, Korkmaz B, et al. Mean red blood cell volume loss in tonsillectomy, adenoidectomy, and adenotonsillectomy. Int J Pediatr Otorhinolaryngol. 2006;70(5):835–41.
12. Prasad KC, Prasad SC. Assessment of operative blood loss and the factors affecting it in tonsillectomy and adenotonsillectomy. Indian J Otolaryngol Head Neck Surg. 2011;63(4):343–8.
13. Simsek G, Karacayli C, Ozel A, Arslan B, Muluk NB, Kilic R. Blood parameters as indicators of upper airway obstruction in children with adenoid or adenotonsillar hypertrophy. J Craniofac Surg. 2015;26(3):e213–6.
14. Gümüssoy M, Atmaca S, Bilgici B, Unal R. Changes in IGF-I, IGFBP-3 and ghrelin levels after adenotonsillectomy in children with sleep-disordered breathing. Int J Pediatr Otorhinolaryngol. 2009;73(11):1653–6.

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Investigation Of the Protective and Therapeutic Effects of Diphenhydramine in An In Vitro Parkinson's Model

Difenhidramin'in İn Vitro Parkinson Modelinde Nöroprotektif ve Terapötik Etkilerinin Belirlenmesi

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Abstract

Objective: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. Neuroprotective treatments are becoming more and more necessary due to the growing prevalence of Parkinson's disease (PD), and these are being investigated as a means to slow the disease's progression. Diphenhydramine (DPH), acting as a histamine 1 receptor antagonist, crosses the blood-brain barrier and exerts effects on the central nervous system. The aim of the present study is to evaluate the neuroprotective and therapeutic effects of DPH in an in vitro PD model induced by 6-hydroxydopamine (6-OHDA).

Materials and Methods: An in vitro PD model was established in Glioblastoma (U-118 MG) cells using 6-OHDA. DPH was applied at three different concentrations before and after 6-OHDA application. The protective effect of DPH was evaluated by assessing cell viability using the XTT cell proliferation assay. The results were analyzed using statistical analysis methods.

Results: The present study demonstrated that dose-controlled administration of DPH has both neuroprotective and therapeutic effects on an in vitro Parkinson's model established with 6-OHDA in the U-118MG cell line. According to our findings, DPH at concentrations of 1, 10, and 100 µM significantly increased cell viability compared to the 6-OHDA control group. DPH at 1 and 10 µM concentrations showed important potential for therapeutic and neuroprotective use.

Conclusion: The in vitro study indicates that DPH has neuroprotective and therapeutic effects on PD-modeled U-118MG neuronal cells by increasing cell viability. Nevertheless, in vivo studies are needed to evaluate the effects of DPH on animal models of PD.

Keywords: Parkinson's Disease, Glioblastoma U-118MG, Diphenhydramine, 6-hydroxydopamine, Neuroprotective and Therapeutic Effect.

&

Öz

Amaç: Parkinson hastalığı (PH), nörodejeneratif hastalıklardan biri olup dopaminerjik nöronların ilerleyici kaybı ile karakterize edilmektedir. PH'nın yaygınlığının artması nedeniyle nöroprotektif tedavilere olan ihtiyaç artmakta ve bu tedaviler hastalığın ilerlemesini yavaşlatmak amacıyla araştırılmaktadır. Difenhidramin (DFH), histamin 1 reseptör antagonisti olarak etki göstermekte ve kan-beyin bariyerini geçerek merkezi sinir sistemi üzerinde etkili olmaktadır. Çalışmamızda, 6-hidroksidopamin (6-OHDA) ile oluşturulan in vitro PH modelinde, DFH'nin nöroprotektif ve tedavi edici etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Glioblastoma (U-118MG) hücrelerinde 6-OHDA ile in vitro PH modeli oluşturuldu. 6-OHDA uygulamasından önce ve sonra 3 farklı konsantrasyonda DFH uygulandı. DFH'nin koruyucu etkisi için hücre canlılığı, XTT hücre proliferasyon testi kullanılarak incelendi. Sonuçlar, istatiksel analiz yöntemleri ile değerlendirildi.

Bulgular: Çalışmamızda, DFH'nin doz kontrollü uygulamasının, U-118MG hücre hattında 6-OHDA ile oluşturulan in vitro Parkinson modeli üzerinde hem nöroprotektif hem de terapötik etkileri olduğunu göstermiştir. Çalışmamız sonucunda elde ettiğimiz bulgulara göre; DFH'nin 1, 10 ve 100 µM konsantrasyonlarda, 6-OHDA kontrol grubuna kıyasla, hücre canlılığını önemli ölçüde artırdığı bulunmuştur. DFH'nin 1 ve 10 µM konsantrasyonları, terapötik ve nöroprotektif kullanım için önemli bir etki göstermektedir.

Sonuç: Yapılan in vitro çalışma DFH'nin, PH modellenmiş U-118MG nöronal hücrelerin canlılığını arttırarak hücreler üzerinde nöroprotektif ve tedavi edici etkilere sahip olduğunu göstermektedir. Bunun yanında, DFH'nin PH hayvan modelleri üzerindeki etkilerini değerlendirmek için in vivo çalışmalar gereklidir.

Anahtar Kelimeler: Parkinson Hastalığı, Glioblastoma U-118 MG, Difenhidramin, 6-hidroksidopamin, Nöroprotektif ve Terapötik Etki.

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Introduction

Neurodegenerative diseases are those characterized by increased oxidative stress, synapse loss, and cell death and which have a major impact on quality of life (1). Diseases of the degenerative neurological system have a significant impact on global populations' health and well-being. Three of the most prevalent neurodegenerative diseases include Parkinson's disease (PD), Alzheimer's disease, and amyotrophic lateral sclerosis. PD is the second most common neurodegenerative disease, with approximately 6 million patients globally (2).

PD is more common as people age, especially a significant rise appearing around age 65 (3). PD is defined by the loss of dopaminergic neurons in the substantia nigra, the part of the brain region responsible for producing of the neurotransmitter dopamine, resulting in decrease of dopamine within the synaptic cleft (4). The most noticeable symptoms of the condition as it progresses are those that are associated with movement and motion, such as rigidity, tremor, postural instability, slowness of movement, gait, and walking difficulties (5). However, wide range of many other neurotransmitter systems are also affected in PD also there is some evidence for the involvement of the histaminergic system (6-8). Many approaches have been studied for the treatment of PD. Until a dramatic decrease in dopamine levels was demonstrated in the brains of patients dying of PD, treatment of this disease was an empirical one, based on incidental observations of medications prescribed for other purposes and, to a lesser extent, just for symptoms (9,10). Levodopa is used in practice; however, motor fluctuations and dyskinesias make the long-term use of levodopa challenging. Furthermore, thanks to their antiparkinsonian effects, the antihistamine benadryl, the antiviral drug amantadine, amphetamine and apomorphine are also used; however, their usage has been limited due to side effects and low efficacy (11-14). Therefore, targeting non-dopaminergic systems may be a helpful alternative method to improve efficacy and motor issues in PD (15).

Histamine is a vital neurotransmitter in the central nervous system that plays a key role in learning, memory, motor, neuroendocrine, and inflammation responses. It is primarily present in mast cells and basophils and is an essential inflammatory intermediary in peripheral tissue allergies and inflammatory reactions (16,17). Histamine is found in the bodies of many species and regulates a variety of physiological activities including smooth muscles, the gastrointestinal, cardiovascular, and immunological systems, as well as central and peripheral neurons (18). Four metabotropic receptor types—histamine H1, H2, H3, and H4—have been identified as a result of recent advancements in drugs that target histamine receptors for a variety of illnesses (19). The histamine H1 receptor, which is highly concentrated in several brain regions, impacts attention, sleep-wake rhythm, wakefulness, and cognition in the hypothalamus, amygdala, thalamus, and cortex (20). Diphenydramine (DPH) primarily acts by antagonizing the histamine 1 receptor, although it also has additional mechanisms of action (21). Chemical structure of DPH is presented in Figure 1. DPH, a first-generation antihistamine drug, can cross the blood-brain barrier and because of it has effects on the central nervous system (20-22). DPH protects the brain following traumatic brain injury by reducing oxidative stress, cerebral edema, and neuronal degeneration (23). After DPH reaches the brain, central H1-receptors are triggered, causing dizziness, drowsiness, convulsions and sedation (24-26). DPH, combined with L-dopa, amantadine or selegiline, was previously used in anesthesia to minimizing tremor symptoms in Parkinson's patients undergoing ophthalmic surgery, as well as an emergency treatment for extrapyramidal side effects created by street drugs and antipsychotics (27-31).

Although there is research on the neuroprotective effects of histamine receptor antagonists in PD, the scope and diversity of these studies are limited. There have been no studies on the neuroprotective effects of DPH on PD. Therefore, in this study, we investigated the neuroprotective and therapeutic effects of DPH, a powerful histamine 1 receptor antagonist that can cross the blood-brain barrier, in an in vitro PD model.

Materials and Methods

Cell Culture

Glioblastoma (U-118MG) cell line was obtained from the American Type Tissue Culture Collection (ATCC, ATCC, Manassas, VA, USA) and cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) (Gibco/BRL, Gaithersburg, MD, USA) supplemented with 1% Penicillin-Streptomycin (Gibco/BRL,

Gaithersburg, MD, USA) 1% L-glutamine (Hyclone) and %10 Fetal Bovine Serum (FBS) (Gibco/BRL, Gaithersburg, MD, USA) at 37°C and 5% CO2. An inverted microscope was used to observe the growth of the cells every day. The cells were passaged by diluation whenever they reached a confluence of about 75-80%.

Determination of suitable 6-OHDA and DPH concentration in medium

When choosing the appropriate concentrations of 6-OHDA (50 μM) and DPH (1 μM, 10 μM, 100 μM) for the study, we looked at concentrations that had been tried out in other investigations and whose efficacy we had independently verified (32-34). To precisely determine the therapeutic and protective concentrations of DPH, at least three repetitions were carried out. Based on the analysis, care was taken to make sure that the results of the three repetitions are consistent with one another.

Cell Viability Assay

The XTT (2,3-bis [2-methoxy-4-nitro–5-sulfophenyl]-2H-tetrazolium-5-carboxyanilide salt) method was employed to assess the proliferation and vitality of cells (35). U-118MG cells were seeded into 96-well plates and were cultivated overnight. The medium in the plates was removed after 24 hours. An in vitro model of PD was established by adding 50 μM of 6-OHDA to each well in DMEM without phenol red. Three different concentrations (1, 10 and 100 μM) of DPH were administered. To assess the protective effects of DPH, it was administered 4 hours before 6-OHDA and to evaluate its therapeutic effects, it was administered 4 hours after 6-OHDA. 20 hours were spent incubating. After the culture time was over, XTT solution (Cell Proliferation Kit II, Sartorius, Israel) was added to the wells and left for 4 hours. A microplate reader (Thermo Scientific MultiskanTM FC, Finland) was used to determine the absorbance values at 450 nm wavelength at the end of the experiment.

Statistical analysis

For the stand-alone DPH application, a one-way ANOVA test was performed, followed by multiple comparisons using Dunnett's post hoc test. Results were evaluated at a significance level of $p<0.05$. For comparisons before and after 6-OHDA application, a one-way ANOVA test was conducted, with pairwise comparisons performed using Tukey's post hoc test. The significance level was again set at $p<0.05$. All statistical analyses were conducted using GraphPad Prism version 10.4.0.621 (GraphPad Software, San Diego, CA, USA). Results were reported in APA format, with statistical significance levels indicated as follows: $p<0.05$; 0.05 (*), 0.01 (**), 0.001 (***).

Results

According to our findings, when applied alone, high doses of DPH reduced cell viability by 4.8% (Figure 2.), but when DPH is used together with 6-OHDA, it increases cell viability compared to 6-OHDA alone. In this case, DPH administered pre-treatment to 6-OHDA demonstrated protective effects of 11.7%, 10.2%, and 2.6% at 1 μM, 10 μM, and 100 μM concentrations, respectively (Figure 3.A.). Similarly, when DPH was administered post-treatment 6-OHDA, an increase in cell viability was also observed (Figure 3.B.). At 1 μM and 10 μM concentrations, therapeutic effects with cell viability increases of 10.2% and 6.9%, respectively, were observed; however, at 100 μM, cell viability decreased by 5.3%. Based on these results, the 1 μM and 10 μM concentrations are identified as the most suitable levels.

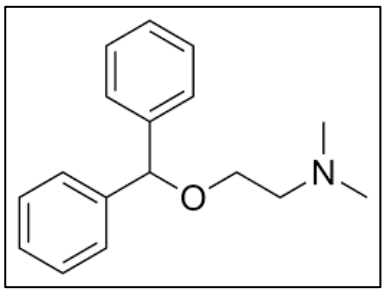

Figure 1. Chemical structure of Diphenhydramine (DPH).

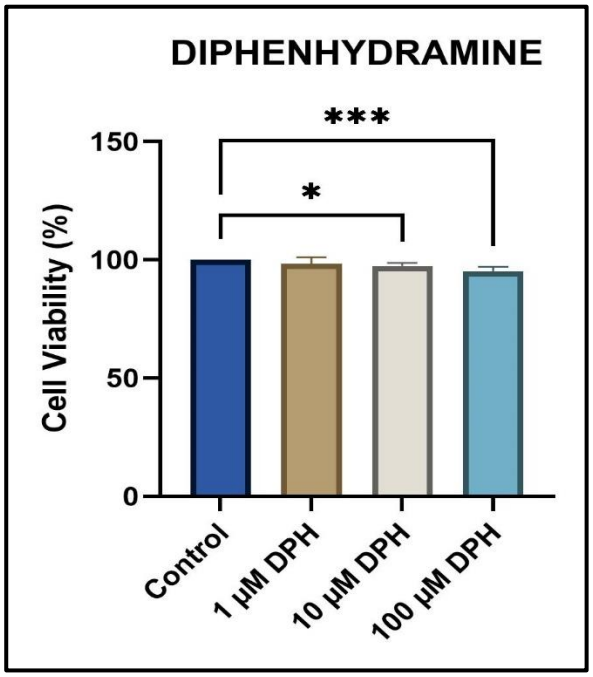

Figure 2. Effect of Diphenhydramine (DPH) alone on cell viability. The data are expressed as means of percentages ± SD (n=8). *: P < 0.05, ***: P< 0.001.

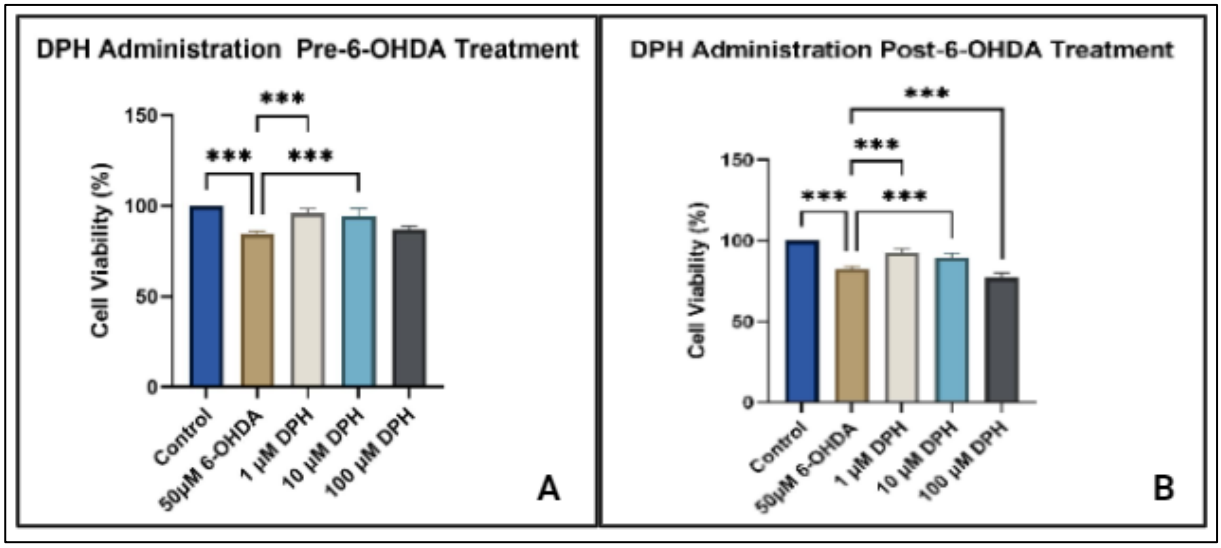

Figure 3. Comparative analysis of Diphenhydramine (DPH) effects on cell viability pre administration of 6-OHDA treatment (A) and post administration of 6-OHDA treatment (B).

Discussion

In the present study, the objective of our investigation was to assess the neuroprotective and therapeutic properties of DPH against 6-OHDA-induced PD in U-118MG cells. In the present study, we found that DPH at concentrations of 1 and 10 µM has neuroprotective and therapeutic effects; in contrast, a high concentration of DPH (100 µM) decreases cell viability.

A sizable section of the population is still afflicted by neurodegenerative illnesses today. PD is one of the most prevalent of them. The oxidative damage brought on by the production of free radicals is the origin of the calcium channel anomalies, glial cell excitation, mitochondrial malfunction and alpha-synuclein deposits observed in PD (36). Numerous processes are being used to treat the disease's symptoms, even though its causes are still not entirely understood. Hence, experimental PD models, both in vivo and in vitro, that can replicate important aspects of the dopaminergic system and recapitulate the disease phenotype are therefore crucial for studying early events of disease genesis and progression (37). In vitro models containing 6-OHDA,

1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium (MPP+), Rotenone and Paraquat are some of the examples used in the treatment of PD (38). A helpful method for researching the molecular processes linked to neuronal death in PD is neuronal exposure to 6-OHDA. 6-OHDA promotes neuronal damage and death by raising oxidant levels and disrupting the mitochondrial respiratory chain. González et al. showed that human neuroblastoma cells exposed to 6-OHDA in vitro had a loss of membrane integrity, an increase in cellular ROS levels, and a decrease in mitochondrial metabolic activity. In this study, we used 6-OHDA as a model. The effects of 6-OHDA on cell viability showed similar results to those of González and colleagues (39).

Furthermore, there is some proof that PD is associated with the histaminergic system and the study findings have demonstrated a large increase in histamine levels in the substantia nigra, putamen, and globus pallidus of PD patients (40). Presence of histamine may be induced in the globus pallidus, putamen, and substantia nigra by a variety of factors, including increased histaminergic fiber density (41, 42). To stop the onset of neuronal degeneration in the case of PD, it can be crucial to shield neuronal cells from excessive histamine levels. Drugs designed to have an antihistaminic effect have been shown to have anti-Parkinsonian effects primarily because they have the pharmacological characteristic of blocking muscarinic neurotransmission (43). Studies indicate that DPH, an antihistamine with anticholinergic properties, can be used in the treatment of PD (44). Histamine type 1 and 2 receptor (H1/2r) antagonists, particularly DPH and cimetidine, have been shown by Lin et al. to improve skin permeability barrier homeostasis when applied topically (45). Pan et al., evaluated the protective effect of DPH against traumatic brain injury (TBI) in light of its antioxidant and anti-inflammatory effects in their animal study. Accordingly, DPH demonstrated a neuroprotective role against TBI by showing improvement in neuronal survival at the tested dose and by attenuating oxidative stress, inflammation and mitochondrial apoptosis pathways (23). Upon reviewing the current literature, we found that in vivo studies on the cytotoxicity of DPH in cancer research show similarities to our in vitro studies (46). However, it has not been directly included in in vitro cell viability studies with DPH. Therefore, in our study, we determined the DPH concentrations based on a previous study we conducted and relevant reference articles (32-34). While looking for neuroprotective effects, we also look for therapeutic effects of the DPH on the Parkinson's cell model for enriching and expanding our research on DPH. And in our research, with dose-controlled therapeutic effects for PD at 1 and 10 μM DPH we find significant effect for therapeutic use.

Conclusion

These results show that DPH has both protective as well as therapeutic aspects against damage effected by cells as result of exposure to 6-OHDA. The implications emphasize the prospective use of DPH as a neuroprotective agent. For the treatment of at least some PD symptoms, targeting H1 receptor that influence effects of histamine may be helpful. This finding may help in the development of new therapies for PD and gives clues to the pathophysiology and possibly also etiology in PD. Also, further studies are required to evaluate the effects of DPH in animal models of PD. Moreover, the cytotoxicity that has been observed implies that DPH might dose-dependently control the survival of glioblastoma cells. More studies should be carried out to ascertain how exactly DPH affects glioblastoma cells and its efficacy as an adjuvant therapy in conjunction with glioblastoma treatment protocols.

Ethics Committee Approval: Ethics Committee Approval was not required for this article because it solely involved the use of commercially available cell lines and did not include any human, animal, or materials derived from them.

Informed Consent: Human volunteers were not used in the study.

Conflict of Interest: Authors declared no conflicts of interest.

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References

1. Starkov AA. The role of mitochondria in reactive oxygen species metabolism and signaling. Ann N Y Acad Sci. 2008;1147:37-52.
2. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. Lancet Neurol. 2021;20(5):385-97.
3. Van Den Eeden SK, Tanner CM, Bernstein AL, Fross RD, Leimpeter A, Bloch DA, et al., Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. Am J Epidemiol. 2003;157(11):1015-22.
4. Marino BLB, de Souza LR, Sousa KPA, Ferreira JV, Padilha EC, da Silva CHTP, et al. Parkinson's Disease: A review from pathophysiology to treatment. Mini Rev Med Chem. 2020;20(9):754-67.
5. Opara J, Małecki A, Małecka E, Socha T. Motor assessment in Parkinson's disease. Ann Agric Environ Med. 2017;24(3):411-15.
6. Lloyd KG, Möhler H, Heitz P, Bartholini G. Distribution of choline acetyltransferase and glutamate decarboxylase within the substantia nigra and in other brain regions from control and Parkinsonian patients. J Neurochem. 1975;25(6):789-95.
7. Coelho MH, Silva IJ, Azevedo MS, Manso CF. Decrease in blood histamine in drug-treated parkinsonian patients. Mol Chem Neuropathol. 1991;14(2):77-85.
8. Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Research. 1983;275(2):321-8.
9. Ehringer H, Hornykiewicz, O. Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system. Klin Wochenschr. 1960;38:1236-9.
10. Carlsson A, Lindqvist M, Magnusson T, Waldeck B. On the presence of 3-hydroxytyramine in brain. Science. 1958;127(3296):471.
11. Schwab RS, Amador LV, Lettvin JY, Apomorphine in Parkinson's disease. Trans Am Neurol Assoc. 1951;56:251-3.
12. Budnitz J. The use of benadryl in Parkinson's disease; a preliminary report of eight cases. N Engl J Med. 1948;238(25):874.
13. Schwab RS, England Jr AC, Poskanzer DC, Young RR. Amantadine in the treatment of Parkinson's disease. Jama. 1969;208(7):1168-70.
14. Kopin IJ. The pharmacology of Parkinson's disease therapy: an update. Annu Rev Pharmacol Toxicol. 1993;33: 467-95.
15. Jenner P. Treatment of the later stages of Parkinson's disease - pharmacological approaches now and in the future. Transl Neurodegener. 2015;4:3.
16. Kim YS, Kim YB, Kim WB, Yoon BE, Shen FY, Lee SW, et al. Histamine resets the circadian clock in the suprachiasmatic nucleus through the H1R-CaV 1.3-RyR pathway in the mouse. Eur J Neurosci. 2015;42(7):2467-77.
17. Hu W, Chen Z. The roles of histamine and its receptor ligands in central nervous system disorders: An update. Pharmacol Ther, 2017;175:116-32.
18. Falkenstein M, Elek M, Stark H. Chemical probes for Histamine receptor subtypes. Curr Top Behav Neurosci. 2022;59:29-76.
19. Sharma A, Muresanu DF, Patnaik R, Menon PK, Tian ZR, Sahib S, et al. Histamine H3 and H4 receptors modulate Parkinson's disease induced brain pathology. Neuroprotective effects of nanowired BF-2649 and clobenpropit with anti-histamine-antibody therapy. Prog Brain Res. 2021;266:1-73.
20. Sadek B, Saad A, Sadeq A, Jalal F, Stark H. Histamine H3 receptor as a potential target for cognitive symptoms in neuropsychiatric diseases. Behav Brain Res. 2016;312:415-30.
21. Church MK, Church DS. Pharmacology of antihistamines. Indian J Dermatol. 2013;58(3):219-24.
22. Lieberman P. Histamine, antihistamines, and the central nervous system. Allergy Asthma Proc. 2009;30(5):482-6.

23. Pan W, Cao Z, Liu D, Jiao Y. Protective effect of Diphenhydramine against traumatic brain injury in rats via modulation of oxidative stress and inflammation. Pharmacology. 2020;05(1-2):47-53.
24. Köppel C, Ibe K, Tenczer J. Clinical symptomatology of diphenhydramine overdose: an evaluation of 136 cases in 1982 to 1985. J Toxicol Clin Toxicol. 1987;25(1-2):53-70.
25. Nicholson AN. Antihistamines and sedation. Lancet. 1983;2(8343):211-2.
26. Gengo F, Gabos C, Miller JK. The pharmacodynamics of diphenhydramine-induced drowsiness and changes in mental performance. Clin Pharmacol Ther. 1989;45(1):15-21.
27. Demetropoulos S, Schauben JL. Acute dystonic reactions from "street Valium". J Emerg Med. 1987;5(4):293-7.
28. Elliott ES, Marken PA, Ruehter VL. Clozapine-associated extrapyramidal reaction. Ann Pharmacother. 2000;34(5):615-8.
29. Pranzatelli MR, Mott SH, Pavlakis SG, Conry JA, Tate ED. Clinical spectrum of secondary parkinsonism in childhood: a reversible disorder. Pediatr Neurol. 1994;10(2):131-40.
30. Scotti G. Treatment of Parkinson's syndrome with L-dopa associated with diphenhydramine hydrochloride and amantadine hydrochloride. Sist Nerv. 1970;22(2):144-52.
31. Nicholson G, Pereira AC, Hall GM. Parkinson's disease and anaesthesia. Br J Anaesth. 2002;89(6):904-16.
32. Okura T, Higuchi K, Kitamura A, Deguchi Y. Proton-coupled organic cation antiporter-mediated uptake of apomorphine enantiomers in human brain capillary endothelial cell line hCMEC/D3. Biol Pharm Bull. 2014;37(2):286-91.
33. Kim J, Song JH. Inhibitory effects of antihistamines, diphenhydramine and chlorpheniramine, on proton currents in BV2 microglial cells. Eur J Pharmacol. 2017; 798:122-8.
34. Kurt AH, Oztabag CK, Sevinc UZ, Kalfa I. Exploring the protective and therapeutic effects of Spinorfin in an in vitro Parkinson's model. Istanbul Medipol University 11th Cellular Neuroscience Days. 2024.
35. Dinc E, Ayaz L, Kurt AH. Protective effect of combined caffeic acid phenethyl ester and bevacizumab against hydrogen peroxide-induced oxidative stress in human RPE Cells. Curr Eye Res. 2017;42(12):1659-66.
36. Cerri S, Mus L, Blandini F. Parkinson's disease in women and men: what's the difference? J Parkinsons Dis 2019;9:501–15.
37. Schüle B, Pera RAR., Langston, JW. Can cellular models revolutionize drug discovery in Parkinson's disease? Biochimica et Biophysica Acta, 2009;1043–51.
38. Altunlu Ö, Topatan E, Al-yaqoobi Z, Burul F, Bayram C, Sezen S, Ferah Okkay I, Okkay U, Hacimuftuoglu A. Experimental Models in Parkinson's Disease: Advantages and Disadvantages. Ağrı Med J. 2024;2(2): 80-7.
39. Iglesias González PA, Conde MA, González-Pardo V, Uranga RM, Salvador GA. In vitro 6-hydroxydopamine-induced neurotoxicity: New insights on NFκB modulation. Toxicol In Vitro. 2019;60:400-11.
40. Rinne JO, Anichtchik OV, Eriksson KS, Kaslin J, Tuomisto L, Kalimo H, et al. Increased brain histamine levels in Parkinson's disease but not in multiple system atrophy. J Neurochem. 2002;81(5): 954-60.
41. Anichtchik OV, Peitsaro N, Rinne JO, Kalimo H, Panula P. Distribution and modulation of histamine H(3) receptors in basal ganglia and frontal cortex of healthy controls and patients with Parkinson's disease. Neurobiol Dis. 2001;8(4):707-16.
42. Anichtchik OV, Rinne JO, Kalimo H, Panula P. An altered histaminergic innervation of the substantia nigra in Parkinson's disease. Exp Neurol. 2000;163(1):20-30.
43. LeWitt PA, Hong L, Moehle MS. Anticholinergic drugs for parkinsonism and other movement disorders. J Neural Transm (Vienna). 2024 Dec;131(12):1481-94.
44. Gonzalez F. Diphenhydramine may be useful as a palliative treatment for patients dying with Parkinson's disease and tremors: a case report and discussion. Am J Hosp Palliat Care. 2009;26(6):474-5.
45. Lin TK, Man MQ, Santiago JL, Park K, Roelandt T, Oda Y, et al. Topical antihistamines display potent anti-inflammatory activity linked in part to enhanced permeability barrier function. J Invest Dermatol. 2013;133(2): 469-78.
46. Or CR, Su HL, Lee WC, Yang SY, Ho C, Chang CC. Diphenhydramine induces melanoma cell apoptosis by suppressing STAT3/MCL-1 survival signaling and retards B16-F10 melanoma growth in vivo. Oncol Rep. 2016 36(6):3465-71.

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The Relationship Between Radiological and Ultrasonographic Changes and Balance Disorders in Patients with Knee Osteoarthritis

Diz Osteoartriti (OA) Hastalarında Radyografik ve Ultrasonografik Değişikliklerin Denge Bozukluğu ile İlişkisi

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Abstract

Objective: This study aimed to assess the relationship between radiological and ultrasonographic changes and balance disorders in patients with knee osteoarthritis.

Materials and Methods: Clinically and radiologically diagnosed 97 patients with knee osteoarthritis, 33 age and sex matched healthy volunteers were included in the study. Balance was analyzed utilizing the Berg Balance Scale (BBS) and Timed Up and Go Test (TUG). Kellgren Lawrence (KL) scale was used for radiographic staging of knee OA. Mean Femoral cartilage, quadriceps femoris muscle thickness (QFMT), thigh subcutaneous fat thickness (TSFT), QFMT/TSFT, quadriceps femoris (QF) tendon, proximal and distal patellar tendon thickness were evaluated using ultrasonography. The functional level and pain severity of the patients was determined by Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score and Visual Analog Scale (VAS).

Results: Individuals with knee OA showed lower BBS, higher TUG scores (p<0.001 for both). Moderate correlations included negative associations of BBS with WOMAC (ϱ=−0.495 p<0.001) and a positive association of TUG with WOMAC (ϱ=0.428 p<0.001). QFMT/TSFT correlated moderately positive with BBS (ϱ=0.448 p<0.001), while TSFT showed a weak negative correlation with BBS (ϱ=−0.364 p<0.001). The KL score had weak negative correlations with BBS (ϱ=−0.201 p=0.048) and weak positive correlations with TUG (ϱ=0.239 p=0.019), and QFMT correlated weakly with BBS (ϱ=0.238 p=0.019). VAS had a weak negative association with BBS (ϱ=−0.255, p=0.012), while TSFT showed a weak positive correlation with TUG (ϱ=0.275, p=0.006). Regression analysis revealed WOMAC as a significant predictor of BBS (p <0.05).

Conclusion: Radiography and ultrasonography could be predictive of balance disorder and those patients with severe osteoarthritis should have an intensive rehabilitative approach to balance disturbance.

Keywords: Balance Disorder, Knee Osteoarthritis, Radiography, Ultrasonography.

&

Öz

Amaç: Diz osteoartriti (OA) olan bireylerde radyografik ve ultrasonografik değişikliklerin denge bozukluğu ile ilişkisinin araştırılması amaçlandı.

Gereç ve Yöntemler: Klinik ve radyolojik diz OA tanılı 97 hasta ve 33 sağlıklı birey çalışmaya dahil edildi. Bireyler Berg Denge Ölçeği (BDÖ), Zamanlı Kalk Yürü Testi (ZKYT) ile incelendi. Osteoartrit Kellgren Lawrence (KL) skalası ile radyolojik olarak evrelendi. Ultrasonografi ile ortalama femoral kartilaj, quadriceps femoris (QF) kas, uyluk subkutan yağ, QF tendon, proksimal ve distal patellar tendon kalınlıkları, QF kas kalınlığının subkutan yağ kalınlığına oranı değerlendirildi. Diz OA tanılı hastaların ağrı ve fonksiyonel durumları Görsel Analog Skala (GAS) ve Western Ontario ve McMaster Üniversitesi Osteoartrit İndeksi (WOMAC) skoru ile değerlendirildi.

Bulgular: Diz osteoartritli bireylerde BDÖ skorların daha düşük, ZKYT skorları daha yüksek saptandı (her ikisi için p < 0,001). BDÖ ile WOMAC (ϱ = −0,495, p < 0,001) arasında orta düzeyde negatif, ZKYT ile WOMAC arasında pozitif bir ilişki vardı (ϱ = 0,428, p <0,001). QF kas kalınlığının subkutan yağ kalınlığına oranı, BDÖ ile orta düzeyde pozitif bir ilişki gösterirken (ϱ = 0,448, p < 0,001), uyluk subkutan yağ kalınlığının BDÖ ile zayıf negatif bir ilişkisi vardı (ϱ = −0,364, p < 0,001). KL skoru, BDÖ ile zayıf negatif (ϱ = −0,201, p = 0,048) ve ZKYT ile zayıf pozitif ilişki gösterdi (ϱ = 0,239, p = 0,019). QF kas kalınlığı, BDÖ ile zayıf pozitif ilişkiye sahipti (ϱ = 0,238, p = 0,019). GAS, BDÖ ile zayıf negatif bir ilişki gösterirken (ϱ = −0,255, p = 0,012), uyluk subkutan yağ kalınlığı, ZKYT ile zayıf pozitif bir ilişki sergiledi (ϱ = 0,275, p = 0,006). Regresyon analizi, WOMAC'ın BDÖ için anlamlı bir belirleyici olduğunu ortaya koydu (p < 0,05).

Sonuç: Radyografi ve ultrasonografi, denge bozukluklarını öngörmede etkili olabilir ve ileri derecede osteoartritli hastalar, denge bozukluklarını yönetmek için yoğun bir rehabilitasyon yaklaşımına tabi tutulmalıdır.

Anahtar Kelimeler: Denge Bozukluğu, Diz Osteooartriti, Radyografi, Ultrasonografi.

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Introduction

Knee osteoarthritis (OA) is a prevalent and disabling condition, recognized as one of the leading causes of disability among older adults in developed nations (1). In Turkey, studies have shown a symptomatic knee OA prevalence of 20.9% in İzmir among individuals aged 40 and older and 14.8% in urban areas of Antalya among individuals aged 50 and older, with risk factors including age, female gender, certain daily activities, and residential type. (2,3). People with knee OA often experience increased balance issues, likely due to reductions in muscle strength and joint position sense (4). Consequently, treatment programs targeting balance improvements are essential to achieving effective rehabilitation (5).

Radiographic imaging plays a pivotal role in diagnosing OA due to its ability to reveal hallmark pathological alterations such as subchondral sclerosis, joint space narrowing, and osteophyte formation on X-ray. These radiographic alterations allow for the classification of OA depending on the location and seriousness of articular cartilage engagement (6,7). Studies have linked structural imaging findings with functional outcomes, such as balance and gait, with higher KL grades associated with greater fall risk as measured by the Berg Balance Scale (BBS) (6,7). Interestingly, this elevated fall risk was not reflected in Timed Up and Go (TUG) test results, suggesting a potential discrepancy between various balance assessment methods (6).

Beyond knee OA, studies on related conditions, such as multiple sclerosis (MS) and Parkinson's disease (PD), provide additional insight into the impact of cartilage degeneration on balance. For instance, ultrasonographic assessments of knee degeneration in MS patients show more pronounced femoral cartilage degeneration compared to healthy controls. However, within the MS group, no significant correlations were found between cartilage degeneration grade and functional scores from the Visual Analog Scale (VAS), BBS or Western Ontario and McMaster University Osteoarthritis Index (WOMAC) (8). Similarly, research into PD revealed that distal femoral cartilage thickness was notably lower in severe PD cases than in healthy individuals. This ultrasonographic evidence suggests early cartilage damage in PD, with a progressive decrease in cartilage thickness as the disease advances (9).

Studies have reported that individuals with knee OA show deficits in standing balance and proprioception, as observed through both clinical assessments and laboratory measurements (4,10–15). Insufficient or inaccurate proprioceptive feedback from the knee joint negatively impacts both static and dynamic balance control in these individuals. Additionally, factors such as muscle strength, OA severity on X-rays, knee alignment, pain levels, and proprioceptive accuracy further influence balance in those with knee OA. Improved standing balance has been associated with greater quadriceps strength, more advanced radiographic disease, reduced varus alignment, lower pain levels, and enhanced proprioception (16,17). Previous studies have also explored the relationship between pain and radiological findings using MRI (Magnetyic Resonance Imaging) and ultrasonography (USG) (18,19). A review analyzing the effects of balance training in knee OA patients found that balance exercises significantly enhance both balance and functionality. This underscores the importance of identifying balance impairments in knee OA to better target and optimize treatment (20).

Our study aimed to delve into the relationship between KL staging, ultrasonographic assessments, and balance metrics in knee OA patients. Unlike previous studies, we seek to determine if combining radiographic and ultrasonographic findings can more accurately predict balance impairments, providing a more holistic understanding of knee OA progression and its effects on postural stability. This could offer new insights for more targeted therapeutic approaches in clinical settings.

Materials and Methods

Tsonga et al. found the fear of falling among patients with OA to be 82.4%, while this rate ranged from 20.8% to 85% among elderly patients (21). Based on these rates, assuming a fear of falling rate of 60% in the control group and 82.4% in osteoarthritis patients, with a critical z value of 1.645, 80% power, and a significance level (α) of 0.05, a minimum of 94 volunteers in the patient group and 32 in the control group are required. This prospective and cross-sectional study was contained a total of 97 individuals between the ages of 50 and 70 diagnosed with knee OA based on the criteria found by the American College of Rheumatology (22) and 33 healthy individuals as control. Prior to participation, all individuals were notified about the study procedure

and written and verbal consent was acquired. This study approved by Ethics Committee of Ankara Numune Health Education and Research Hospital (approval numbered 2425/2018 dated 07.02.19) and the study followed the tenets of the Helsinki Declaration. All procedures adhered to the ethical standards of the responsible committee on human experimentation (institutional and national) and complied with the Helsinki Declaration of 1975, as revised in 2008.

The inclusion of patients aged 65 to 70 with knee OA in this study is important because balance problems often become more pronounced in this age range due to age-related physiological changes, including muscle weakening and altered proprioception. This age group is more susceptible to these balance impairments, which are further exacerbated by OA. By studying individuals within this age bracket, we aim to gain a clearer understanding of how OA-related changes impact balance and function, which can provide valuable insights for developing targeted interventions for fall prevention and mobility improvement in older adults with OA (23).

Trauma history to that knee in the last 6 months, knee prosthesis, osteotomy, arthroscopy and any surgical operation on the lower extremity in the past, those who have received intra-articular steroid injection within 4 weeks, those who have a neurological disease that may cause severe balance disorders (Parkinson's disease, stroke history, multiple sclerosis, epilepsy, cardiac syncope), those with a history of drug use that may cause balance disorders, those with severe visual impairment, those with depressive mood, those with severe respiratory, central, peripheral, vascular and subjects with uncontrolled metabolic problems, patients who need assistive devices for ambulation and those who did not sign the informed consent form were excluded from the study. The demographic data, including age, gender, weight, height, education, occupation and presence of additional diseases, was noted. Body mass index (kg/m2) (BMI) was computed.

Asssesment Criteria

Radiographic evaluation was performed using the KL scale on anteroposterior and lateral knee radiographs by the researchers. The early stages, typically KL grades 0, 1, and 2, are associated with minimal to moderate changes in the joint. These early grades typically correlate with mild symptoms or minimal functional limitations. As the disease progresses, KL grades 3 and 4 reflect more severe joint degeneration, with significant narrowing of the joint space, larger osteophytes, and possible deformities (24).

A GE P5 Model Ultrasonography device (GE Healthcare, Chicago, United States) with a 7-12 MHz linear probe for evaluations. The measurements were conducted by a researcher with over 2 years of experience in musculoskeletal ultrasonography, under the supervision of an individual with more than 8 years of expertise in the field. Quadriceps femoris muscle thickness (QFMT), QFMT/thigh subcutaneous fat thickness (TSFT), quadriceps femoris muscle tendon thickness (QFMTT), proximal and distal patellar tendon thickness, and femoral cartilage (FC) thickness were assessed. Care was taken to avoid unnecessary pressure during measurements to prevent probe interference with underlying tissue. Every measurement was carried out three times, the mean was recorded. QFMT and TSFT were assessed with the patient in the supine position, probe in the transverse plane, positioned 15 cm proximal to the midpoint of the patella (Figure 1). Distal FC thickness, medial, intercondylar and lateral FC thickness measurements were measured with the knee maximally flexed, in the transverse plane perpendicular to the femur and the average was recorded (Figure 2). QFTT measurement was conducted the knee bent at an angle of 20-30 degrees, in the sagittal plane from just before the QF tendon attachment to the patella. Proximal tendon thickness was measured at the lower end of the patella, and distal proximal tendon thickness was measured where the tuberosity attaches to the tibia.

The functional level of the patients due to knee OA was evaluated using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Pain was evaluated with 5, stiffness with 2, and functional level with 17 questions. For each measurement, questions were scored between 0-4 and the total score was determined (total score min 0, max 96). Turkish validity and reliability study of the index was carried out (25).

Participants' pain levels were evaluated with the Visual Analogue Scale (VAS) on a scale of 0-10 cm (0: no pain, 10: the worst pain imaginable). VAS was utilized to assess the knee pain experienced by patients over the past week. The patient was instructed to quantify the severity of his pain on a horizontal line marked between 0 and 10 (26).

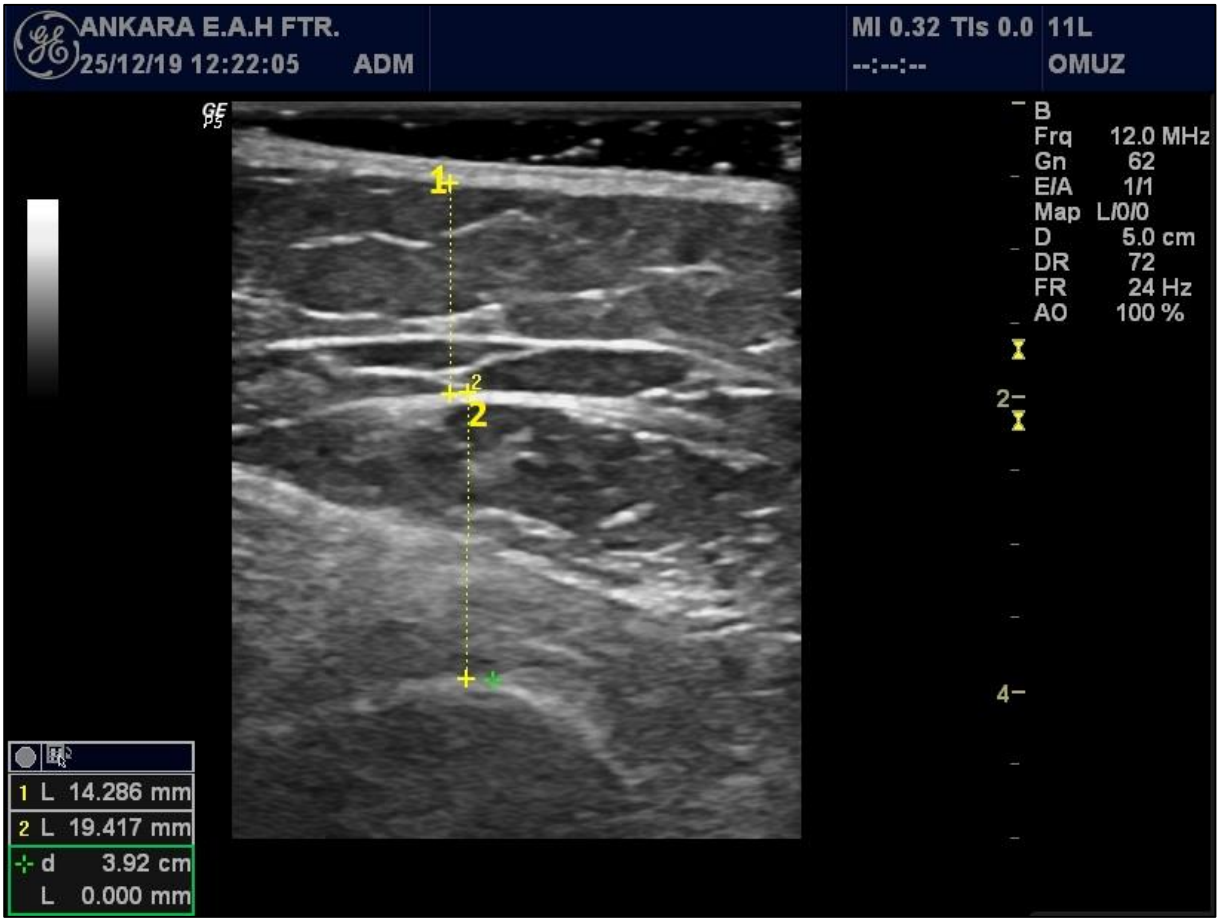

Figure 1. Ultrasonographic measurement of quadriceps femoris muscle thickness (2) /thigh subcutaneous fat thickness (1)

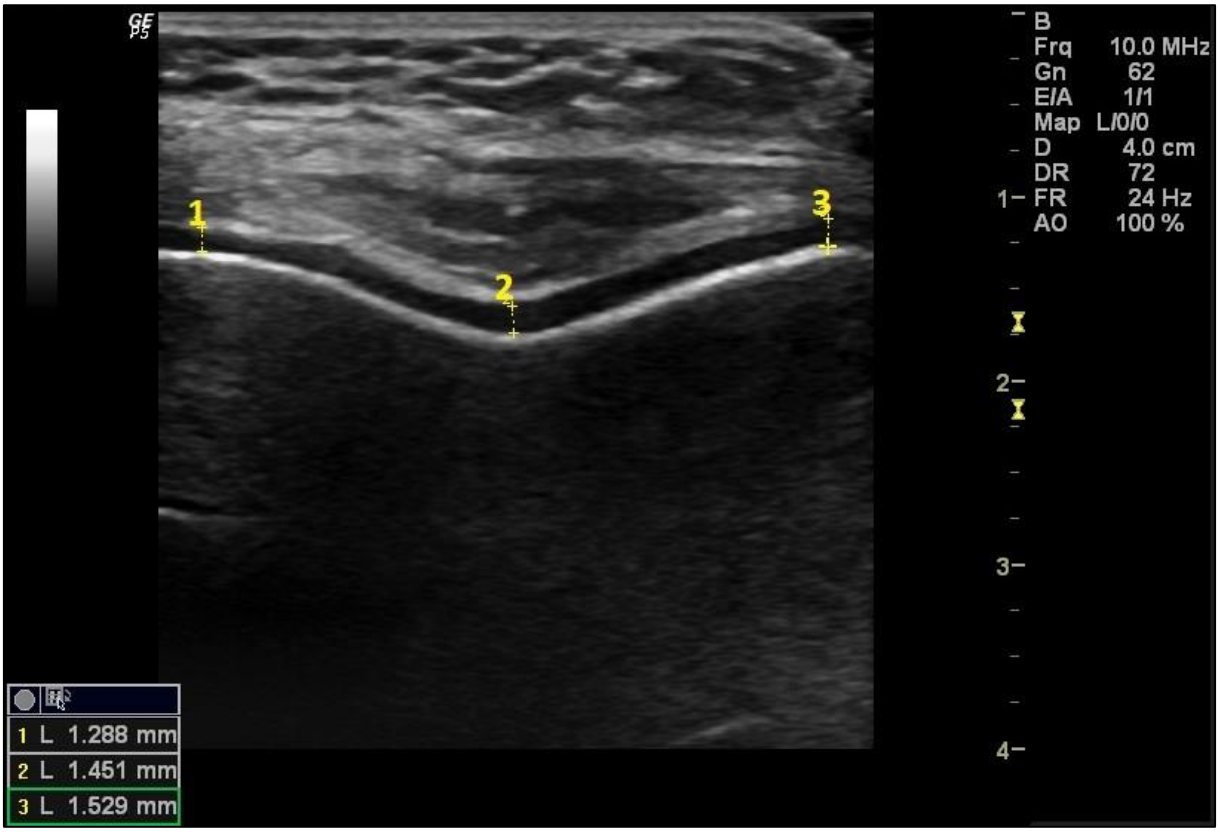

Figure 2. Ultrasonographic measurement of distal femoral cartilage thickness; medial (1), intercondylar (2) and lateral (3) femoral cartilage thickness

Participants' static and dynamic balances were evaluated with the BBS, and their dynamic balance and mobility with the TUG. BBS is utilized to evaluate both static and dynamic balance. The BBS has been used in many studies in older adults, Parkinson's patients, patients with osteoporosis, and those with a history of stroke, and is considered the gold standard in the evaluation of functional balance (27–29)Turkish validity and reliability study was conducted (30). BBS consists of 14 different questions. The patient is evaluated by the observer while doing these activities and scored between 0-4. In this scoring, while a score of 4 symbolizes performing the activity without any support, a score of 0 symbolizes full support or the inability to perform the activity at all. The highest total score is 56 and indicates perfect balance. If a patient scores between 0-20, they are wheelchair-dependent, while a score between 21-40 indicates the ability to walk with assistance. Independence in mobilization activities is considered for scores between 41 and 56. Scores below 45 are related to increased fall risk (31).

TUG, is primarily a functional test that assesses dynamic balance, walking speed and mobility can be swiftly assessed. The duration required for the patient to rise from the chair, walk 3 meters, return and sit is recorded. The average of 3 tests is taken. A shorter TUG indicates better functional performance and. Values of 13.5 seconds and above were linked to an increased chance of falling (32).

Statistical analyzes were performed with SPSS version 21.0 (IBM, Armonk, NY, USA). The normality assumption of variables was assessed utilizing the Kolmogorov-Smirnov test. For comparisons between groups, the Mann-Whitney U test was employed for non-parametric variables, while the Student's t-test was utilized for parametric variables. The Chi-Squared test was applied to assess categorical variables. In correlation analysis, either Pearson or Spearman correlation tests were chosen based on the distribution of the data. Regression analysis was performed for BBS and TUG scales that showed significant results in the correlation analysis. A significance level of $p<0.05$ was considered statistically significant for all tests.

Results

The study was completed with 97 individuals in the knee OA group and 33 people in the control group. There was no significant difference between the knee OA group and the control group with respect to age, gender, height, and presence of additional diseases ($p>0.05$, for all). Weight and BMI were discovered to be markedly greater in the knee OA group ($p<0.05$). In individuals with knee OA, BBS scores were discovered to be lower and TUG scores were higher ($p <0.001$ for both). Demographic data and balance impairment evaluations of knee OA and control groups is demonstrated in Table 1.

For KL scores, 75.8% of the control group had a score of 0, while none of the OA group had this score ($p<0.001$). Additionally, 24.2% of the control group had a KL score of 1, compared to 1% in the OA group. In contrast, higher KL scores were observed exclusively in the OA group, with 52.6% having a score of 2, 39.2% a score of 3, and 7.2% a score of 4, with none of the control group falling within these ranges.

In the OA group, correlation analysis revealed no significant differences in BBS scores and in TUG Scores in terms of gender, occupation, or education level. In this study, moderate correlations included negative associations of BBS with WOMAC ($\varrho=-0.495$ $p=0.000$) and age ($\varrho=-0.426$ $p=0,000$), as well as positive associations of TUG with WOMAC ($\varrho=0.428$ $p=0.000$). Additionally, the QFMT/TSFT correlated moderately positive with BBS ($\varrho=0.448$ $p=0.000$), while TSFT showed a weak negative correlation with BBS ($\varrho=-0.364$ $p=0.000$). Weak positive correlations were found between age and TUG ($\varrho=0.379$ $p=0.000$), VAS and TUG ($\varrho=0.242$ $p=0.017$), and BMI with both TUG ($\varrho=0.281$ $p=0.005$) and weak negative correlations BBS ($\varrho=-0.244$ $p=0.016$). Additionally, the KL score had weak negative correlations with BBS ($\varrho=-0.201$ $p=0.048$) and weak positive correlations with TUG ($\varrho=0.239$ $p=0.019$), and QFMT correlated weakly with BBS ($\varrho=0.238$ $p=0.019$). Height demonstrated a weak negative correlation with TUG ($\varrho=-0.251$ $p = 0.013$). Additionally, VAS had a weak negative association with BBS ($\varrho=-0.255$, $p=0.012$), while TSFT showed a weak positive correlation with TUG ($\varrho=0.275$, $p=0.006$). These findings suggest that factors like age, WOMAC, VAS, KL scores, TSFT, QFMT/TSFT and BMI play varying roles in balance and mobility among patients with knee OA (Table 2).

Table 1.
Demographic Data and Balance İmpairment Evaluations of Knee Osteoarthritis Patients and Control Groups

		Control (N=33)	Patient (N=97)	p value
Age (year)		59(54.5-61)	59(54-64)	0.229[a]
BMI (kg/m²)		25.05±2.46	30.74±4.71	**<0.001**[b]
		N(%)	**N(%)**	
Gender	Female	26(%78.8)	86(%88.7)	0.156[c]
	Male	7(%21.2)	11(%11.3)	
Occupation	House wife	5(%15.2)	80(%82.5)*	**<0.001**[c]
	Worker	5(%15.2)	9(%9.3)	
	Officer	15(%45.5)*	1(%1)	
	Other	8(%24.2)*	7(%7.2)	
Educational level	Literate	0(%0)	27(%27.8)*	**<0.001**[c]
	Primary school	10(%30.3)	60(%61.9)*	
	Middle school	0(%0)	2(%2.1)	
	High school	10(%30.3)	6(%6.2)	
	University	13(%39.4)*	2(%2.1)	
BBS		56(55-56)	52(50-54)	**<0.001**[a]
TUG (sn)		9(8-9)	10.5(9-12)	**<0.001**[a]

x̄±SD: Mean ± Standard Deviation,
Md (Q1-Q3): Median (Interquartile Range)
a: Mann-Whitney U test
b: Student's t-test
c: Chi-Square
BMI: Body Mass Index
BBS: Berg Balance Scale
TUG: Timed up and Go Test
*: Statistically significant higher ($p<0.05$)

When the OA group compared with the control group no significant differences were found between the two groups in terms of hypertension, diabetes mellitus, cardiovascular disease, kidney disease, lung disease, and other comorbidities ($p>0.05$ for all).

Table 2.

Correlations Of Balance Assessment Tests with Other Data in Knee Osteoarthritis Patients

Test		Berg balance	TUG
BBS	Rho		**-0.736**
	P		**<0.001**
TUG (sn)	Rho	**-0.736**	
	P	**<0.001**	
Age (years)	Rho	**-0.426**	**0.379**
	P	**<0.001**	**<0.001**
Weight (kg)	Rho	-0.097	0.141
	P	0.343	0.170
Height (m)	Rho	0.167	**-0.251**
	P	0.103	**0.013**
VAS (cm)	Rho	**-0.255**	**0.242**
	P	**0.012**	**0.017**
WOMAC	Rho	**-0.495**	**0.428**
	P	**<0.001**	**<0.001**
KL score	Rho	**-0.201**	**0.239**
	P	**0.048**	**0.019**
MFC thickness (mm)	Rho	0.163	-0.122
	P	0.112	0.233
IFC thickness (mm)	Rho	**0.209**	-0.156
	P	**0.040**	0.127
LFC thickness (mm)	Rho	0.185	-0.114
	P	0.069	0.265
Mean FC (mm)	Rho	**0.212**	-0.161
	P	**0.037**	0.115
QF muscle thickness (mm)	Rho	**0.238**	-0.198
	P	**0.019**	0.052
Thigh subcutaneous fat thickness (mm)	Rho	**-0.364**	**0.275**
	P	**<0.001**	**0.006**
QF tendon thickness(mm)	Rho	0.000	0.090
	P	0.998	0.382
Proximal patellar tendon thickness (mm)	Rho	-0.127	0.180
	P	0.214	0.078
Distal patellar tendon thickness (mm)	Rho	-0.112	0.188
	P	0.276	0.065
QFMT/TSFT	Rho	**0.448**	**-0.356**
	P	**<0.001**	**<0.001**
BMI (kg/m²)	Rho	**-0.244**	**0.281**
	P	**0.016**	**0.005**

BBS: Berg Balance Scale, TUG: Timed up and Go Test, KL: Kellgren Lawrence, MFC: Medial femoral cartilage, IFC: Interconylar femoral cartilage, LFC: Lateral femoral cartilage, Mean FC: Mean femoral cartilage, QF: Quadriceps femoris, QFMT: Quadriceps femoris muscle thickness TSFT: Thigh subcutaneus fat thickness BMI: Body Mass Index
rho: Spearman correlation coefficient.

Regression analysis was performed for BBS and TUG scales that showed significant results in the correlation analysis. A regression analysis was conducted to examine the relationship between WOMAC, VAS, and KL scores and BBS scores. It was found that 49% of the variance was explained ($p<0.001$). WOMAC scores showed a significant relationship with Berg balance scores ($p<0.05$ for all) (Table 3).

Table 3.
Regression Analysis for the BBS Test

	Unstandardized coefficients (B)	SE	Unstandardized coefficients (Beta)	p value	95% CI
(Constant)	55.424	5.757		<0.001	(43.965 to 66.883)
WOMAC	-0.05	0.021	-0.278	***0.016***	(-0.091 to -0.010)
VAS	-0.06	0.201	-0.034	0.767	(-0.459 to 0.340)
KL_skoru	-0.385	0.388	-0.087	0.324	(-1.157 to 0.388)

R2=0,493; 95% CI: Confidence interval for B, SE: standard error, BBS: Berg Balance Scale, WOMAC: Western Ontario and McMaster University Osteoarthritis Index, VAS: Visual Analog Scale, KL: Kellgren Lawrence.

A regression analysis was conducted to examine the relationship between WOMAC, VAS, and KL scores and TUG scores. It was found that 40% of the variance was explained (p<0.001). No significant relationship was found between WOMAC, VAS, and KL scores and TUG scores (p>0.05 for all) (Table 4).

Table 4.
Regression Analysis for the TUG Test

	Unstandardized coefficients (B)	SE	Unstandardized coefficients (Beta)	p value	95% CI
(Constant)	14.679	5.639		0.011	(3.451 to 25.908)
WOMAC	0.018	0.019	0.116	0.355	(-0.020 to 0.056)
VAS	0.000	0.193	0.000	0.998	(-0.385 to 0.385)
KL_skoru	0.264	0.384	0.069	0.495	(-0.502 to 1.029)

R^2=0.397; 95% CI: Confidence interval for B, SE: standard error, TUG: Timed up and Go Test, WOMAC: Western Ontario and McMaster University Osteoarthritis Index, VAS: Visual Analog Scale, KL: Kellgren Lawrence

Discussion

In this study, knee OA patients demonstrated significantly lower BBS scores and higher mobility impairment (TUG) times compared to the control group. The OA group also exhibited higher BMI and weight. Moderate negative correlations were observed between BBS and WOMAC scores, age, and moderate positive correlations between BBS and QFMT/TSFT, as well as between TUG and WOMAC. Weak negative correlations were identified between BBS and VAS, KL score, and BMI, while weak positive correlations were found between TUG and VAS, KL score, TSFT, and BMI. Regression analysis revealed a significant relationship between WOMAC scores and BBS. Conversely, no significant predictors were identified for TUG scores in the regression analysis. Additionally, demographic factors such as gender, occupation, and education level showed no significant differences in BBS or TUG scores. Overall, factors like WOMAC scores, body composition, and age play key roles in influencing balance and mobility in knee OA patients.

The demographic and clinical characteristics of the knee OA group in our study, including mean age, female-to-male ratio, and BMI, align well with findings reported in the general literature. The mean age of participants, as well as the predominance of female patients (88.7%), reflects the commonly observed higher prevalence of OA in older adults and a greater incidence among women, consistent with previous studies.

Furthermore, the significantly higher BMI in the OA group compared to controls is in line with established evidence that links increased BMI to a heightened risk of knee OA due to the added mechanical load on joints and its role as a modifiable risk factor in OA progression (33). These demographic and clinical patterns support the generalizability of our findings to the broader OA population.

Balance disorders have emerged as a significant public health concern, primarily attributed to the heightened risk of falling (34). Individuals with knee osteoarthritis (OA) are more likely to experience falls compared to those without OA (35). In the context of knee OA, the compromised proprioception is not only associated with articular cavity concerns but also stems from the reduction in mechanosensory receptors within periarticular tissues such as ligaments, tendons, and muscles, where sensory innervation is predominant. Due to the decrease in QF strength, postural stability deteriorates, leading to an increased risk of balance issues and incidents of falling in patients with knee OA (15,36).

While Analan et al. found no significant differences in postural stability between KL stage 2 and 3 knee OA patients (37), our study observed that balance decreases with more advanced KL stages, suggesting that KL staging may indeed influence balance as OA progresses. This supports our focus on assessing balance impairments in more severe OA cases, as evidenced through functional measures like the BBS and TUG tests. Our study's results corroborate existing research on the association between knee OA severity and declines in balance and mobility, as seen through functional measures such as the BBS and TUG test. Consistent with research by Ribeiro et al., individuals with higher KL grades exhibited poorer balance, consistent with our observations of reduced BBS scores as OA severity rose (6). However, as highlighted in previous studies, a discrepancy can exist between balance assessment methods, with fall risk not always captured by TUG times despite BBS sensitivity, a pattern also observed in our study (6).

Our study revealed a positive correlation between Balance Berg Scale (BBS) scores and mean femoral cartilage (FC) thickness, suggesting that better balance is associated with greater cartilage thickness. Beyond OA, research on related degenerative conditions like MS and PD offers insights into the broader implications of cartilage degeneration on balance (8). For example, Eroglu et al. found that MS patients exhibited significant femoral cartilage (FC) degeneration, though it did not strongly correlate with balance scores, similar to findings by Uysal et al. for distal FC thickness in PD patients (8). These findings indicate that while cartilage degeneration plays a critical role in balance and mobility in OA, the relationship varies across conditions, reflecting distinct mechanisms affecting physical function. Together, these studies highlight the need for diverse assessment tools to better understand the complex interplay between structural degeneration and functional outcomes in OA and other conditions.

We acknowledge that the primary limitation of our study is the lack of homogeneity in weight and BMI within our patient group, with the knee OA group having higher BMI and weight levels. As a higher BMI is often linked to an increased risk of balance impairments and falls, especially in older adults, due to the added joint stress, reduced mobility, and shifts in the center of gravity associated with excess weight. Secondly, the study group had a predominance of female participants. Ensuring similar gender distributions in future research could help to reveal knee OA related differences more clearly. Including patients aged 65-70 in the study is another limitation, as balance problems often develop within older adults. Our findings demonstrated that the following factors associated with balance function in patients with knee OA: age, VAS, WOMAC, KL score and BMI values, ultrasonographically measured intercondylar FC thickness, mean FC thickness, TSFT, QFMT and QFMT/TSFT. There is a need for studies with groups with different demographic and cultural characteristics to evaluate other factors affecting radiological and ultrasonographic changes in knee OA.

Conclusion

This study highlights balance disorders in knee OA and their significant associations with radiological and ultrasonographic findings. Key metrics like QFMT, QFMT/TSFT and KL scores were correlated with balance measures, and WOMAC emerged as a strong predictor of balance performance. These findings underscore the value of combining imaging and clinical assessments to better understand and address balance impairments in knee OA patients. Additionally, patients with severe OA should undergo an intensive rehabilitative approach to address balance disturbances effectively.

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Numune Health Education and Research Hospital (date: 07.02.2019 and approval number2425/2018).

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

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References

1. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull. 2013;105(1):185–99.
2. Yeşil H. Prevalence of symptomatic knee, hand and hip osteoarthritis among individuals 40 years or older: a study conducted in İzmir city. Acta Orthop Traumatol Turc. 2013;47(4):231–5.
3. Kaçar C, Gilgil E, Urhan S, Arıkan V, Dündar Ü, Öksüz MC, et al. The prevalence of symptomatic knee and distal interphalangeal joint osteoarthritis in the urban population of Antalya, Turkey. Rheumatol Int. 2005;25(3):201–4.
4. Hinman RS. Balance impairments in individuals with symptomatic knee osteoarthritis: a comparison with matched controls using clinical tests. Rheumatology. 2002;41(12):1388–94.
5. Tasci Bozbas G, Sendur OF, Aydemir AH. Primary knee osteoarthritis increases the risk of falling. J Back Musculoskelet Rehabil. 2017;30(4):785–9.
6. Ribeiro IC, Coimbra AMV, Costallat BL, Coimbra IB. Relationship between radiological severity and physical and mental health in elderly individuals with knee osteoarthritis. Arthritis Res Ther. 2020;22(1):187.
7. Yoldas B, Akdemir E, Anil B, Korkmaz E, Kumru D, Yilmaz C, et al. Pain, quality of life, proprioception and physical function in patient with knee osteoarthritis: Comparison of different grades. Medicine Science | International Medical Journal. 2024;13(2):406.
8. Eroglu S, Inal E, Eroglu M, Oruc S, Ulasli A, Cevik H, et al. Ultrasound detection of knee joint degeneration in patients with multiple sclerosis. J Rehabil Med. 2016;48(7):604–8.
9. Uysal A, Guntel M, Demetgül Ö, Çiçek U. Ultrasonographic Evaluation of the Distal Femoral Cartilage Thickness in Parkinson's Patients. J Musculoskelet Neuronal Interact. 2023;23(3):328-37.
10. Knoop J, Steultjens MPM, van der Leeden M, van der Esch M, Thorstensson CA, Roorda LD, et al. Proprioception in knee osteoarthritis: a narrative review. Osteoarthritis Cartilage. 2011;19(4):381–8.
11. Hatfield GL, Morrison A, Wenman M, Hammond CA, Hunt MA. Clinical Tests of Standing Balance in the Knee Osteoarthritis Population: Systematic Review and Meta-analysis. Phys Ther. 2016;96(3):324–37.
12. Sazo-Rodríguez S, Méndez-Rebolledo G, Guzmán-Muñoz E, Rubio-Palma P. The effects of progressive neuromuscular training on postural balance and functionality in elderly patients with knee osteoarthritis: a pilot study. J Phys Ther Sci. 2017;29(7):1229–35.
13. Truszczyńska-Baszak A, Dadura E, Drzał-Grabiec J, Tarnowski A. Static balance assessment in patients with severe osteoarthritis of the knee. Knee. 2020;27(5):1349–56.
14. Lawson T, Morrison A, Blaxland S, Wenman M, Schmidt CG, Hunt MA. Laboratory-based measurement of standing balance in individuals with knee osteoarthritis: A systematic review. Clinical Biomechanics. 2015;30(4):330–42.
15. Kim HS, Yun DH, Yoo SD, Kim DH, Jeong YS, Yun JS, et al. Balance Control and Knee Osteoarthritis Severity. Ann Rehabil Med. 2011;35(5):701.
16. Hunt MA, McManus FJ, Hinman RS, Bennell KL. Predictors of single-leg standing balance in individuals with medial knee osteoarthritis. Arthritis Care Res (Hoboken). 2010;62(4):496–500.

17. Sanchez-Ramirez D, Leeden M, Knol D, Esch M, Roorda L, Verschueren S, et al. Association of postural control with muscle strength, proprioception, self-reported knee instability and activity limitations in patients with knee osteoarthritis. J Rehabil Med. 2013;45(2):192–7.
18. Mermerci BB, Garip Y, Uysal RS, Doğruel H, Karabulut E, Özoran K, et al. Clinic and ultrasound findings related to pain in patients with knee osteoarthritis. Clin Rheumatol. 2011;30(8):1055–62.
19. Kornaat PR, Bloem JL, Ceulemans RYT, Riyazi N, Rosendaal FR, Nelissen RG, et al. Osteoarthritis of the Knee: Association between Clinical Features and MR Imaging Findings. Radiology. 2006;239(3):811–7.
20. Pirayeh N, Kazemi K, Rahimi F, Mostafaee N, Shaterzadeh-Yazdi MJ. The Effect of Balance Training on Functional Outcomes in Patients with Knee Osteoarthritis: A Systematic Review. Med J Islam Repub Iran. 2022;36:107.
21. Tsonga T, Michalopoulou M, Kapetanakis S, Giovannopoulou E, Malliou P, Godolias G, et al. Risk Factors for Fear of Falling in Elderly Patients with Severe Knee Osteoarthritis before and One Year after Total Knee Arthroplasty. Journal of Orthopaedic Surgery. 2016;24(3):302–6.
22. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis Rheum. 1986;29(8):1039–49.
23. Manlapaz DG, Sole G, Jayakaran P, Chapple CM. Risk Factors for Falls in Adults with Knee Osteoarthritis: A Systematic Review. PM&R. 2019;11(7):745–57.
24. Kohn MD, Sassoon AA, Fernando ND. Classifications in Brief: Kellgren-Lawrence Classification of Osteoarthritis. Clin Orthop Relat Res. 2016;474(8):1886–93.
25. Tüzün EH, Eker L, Aytar A, Daşkapan A, Bayramoğlu M. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. Osteoarthritis Cartilage. 2005;13(1):28–33.
26. Johnson EW. Visual Analog Scale (VAS). Am J Phys Med Rehabil. 2001;80(10):717.
27. Qutubuddin AA, Pegg PO, Cifu DX, Brown R, McNamee S, Carne W. Validating the Berg Balance Scale for patients with Parkinson's disease: A key to rehabilitation evaluation. Arch Phys Med Rehabil. 2005;86(4):789–92.
28. Ersoy Y, MacWalter RS, Durmus B, Altay ZE, Baysal O. Predictive Effects of Different Clinical Balance Measures and the Fear of Falling on Falls in Postmenopausal Women Aged 50 Years and Over. Gerontology. 2009;55(6):660–5.
29. Blum L, Korner-Bitensky N. Usefulness of the Berg Balance Scale in Stroke Rehabilitation: A Systematic Review. Phys Ther. 2008;88(5):559–66.
30. Sahin F, Yilmaz F, Ozmaden A, Kotevoglu N, Sahin T, Kuran B. Reliability and Validity of the Turkish Version of the Berg Balance Scale. Journal of Geriatric Physical Therapy. 2008;31(1):32–7.
31. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly: validation of an instrument. Can J Public Health. 1992;83 Suppl 2:S7-11.
32. Freter SH, Fruchter N. Relationship between timed 'up and go' and gait time in an elderly orthopaedic rehabilitation population. Clin Rehabil. 2000;14(1):96–101.
33. Murphy L, Helmick CG. The Impact of Osteoarthritis in the United States. AJN, American Journal of Nursing. 2012;112(3):S13–9.
34. Khalaj N, Abu Osman NA, Mokhtar AH, Mehdikhani M, Wan Abas WAB. Balance and Risk of Fall in Individuals with Bilateral Mild and Moderate Knee Osteoarthritis. PLoS One. 2014;9(3):e92270.
35. Deng Z, Xu J, Long L, Chen F, Chen K, Lu W, et al. Association between hip and knee osteoarthritis with falls: A systematic review and meta-analysis. Int J Clin Pract. 202175(10).
36. Duman I, Taskaynatan MA, Mohur H, Tan AK. Assessment of the impact of proprioceptive exercises on balance and proprioception in patients with advanced knee osteoarthritis. Rheumatol Int. 2012;32(12):3793–8.
37. DORUK ANALAN P. The Evaluation of Relation Between Radiological Grading and Postural Stability, Function, Isokinetic Measurements in Patients with Primary Knee Osteoarthritis. Fiziksel Tıp ve Rehabilitasyon Bilimleri Dergisi. 2019;22(1):7–15.

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Deep Femoral Artery Injury After Conversion Hip Arthroplasty: A Case Report

Kalça Artroplastisi Dönüşümü Sonrası Derin Femoral Arter Yaralanması: Bir Olgu Sunumu

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Abstract

68-year-old male patient is admitted to hospital due to hip pain. He had undergone a surgery for left pertrochanteric fracture 18 days ago in another hospital. A locked plate was used for osteosynthesis which have failed immediately after mobilization. Single stage revision was performed due to implant failure and acute implant related infection. Hematoma formation and persistent wound drainage developed. Angiography identified an injury of deep femoral artery. Angiographic embolization was performed.

If patient experiences recurrent swelling, hematoma and persistent wound drainage, vascular injury should be considered. Angiography should be carried out for early diagnosis. Angiographic embolization provides effective treatment.

Keywords: Hematoma, Deep Femoral Artery, Ct Angiography, Angiographic Embolization, Prosthetic Joint Infection.

&

Öz

68 yaşındaki erkek hasta, kalça ağrısı şikayetiyle hastaneye başvurdu. Hasta, başka bir hastanede 18 gün önce sol taraflı pertrokanterik kırık nedeniyle cerrahi operasyon geçirmişti. Osteosentez için kilitli plak kullanılmış, ancak mobilizasyon sonrası implant hemen başarısız olmuştur. İmplant başarısızlığı ve akut implant ilişkili enfeksiyon nedeniyle tek aşamalı revizyon uygulanmıştır. Hematom oluşumu ve kalıcı yara akıntısı gelişmiştir. Anjiyografi, derin femoral arter yaralanmasını tespit etmiş ve anjiyografik embolizasyon yapılmıştır.

Eğer hastada tekrarlayan şişlik, hematom ve kalıcı yara akıntısı görülürse, vasküler yaralanma düşünülmelidir. Erken tanı için anjiyografi yapılması gerekir. Anjiyografik embolizasyon etkili bir tedavi sağlar.

Anahtar Kelimeler: Hematom, Derin Femoral Arter, BT Anjiyografi, Anjiyografik Embolizasyon, Protez Eklem Enfeksiyonu.

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Introduction

Vascular injuries are rare but devastating complications in total hip arthroplasty (THA). The risk of vascular injury should be kept in mind due to the proximity of major vessels when performing THA. The prevalence of vascular injury in primary THA was reported to be 0.08-0.5% (1). Due to the more complex nature of revision THA the risk is even higher (0.2% - 1.2%) (2). The most common causes for vascular injury are retractor compression, direct penetration during acetabular reaming, screw, and PMMA thermal necrosis (1). Depending on the level and location of vascular injury, it may cause excessive bleeding compartment syndrome, functional loss, hypotensive shock, and even death (3). Postoperative follow-up may reveal the condition, with the patient showing general deterioration, resistant anemia, hypotension, progressive swelling, hematoma formation, persitant wound drainage and severe pain.

In this case report, a patient who underwent revision THA due to implant failure and infection, persistent hematoma and bleeding caused by pseudoaneurysm of the deep femoral artery will be discussed. The patient was informed that the data concerning the case would be submitted for publication and informed consent was obtained.

Case Presentation

A 68-year-old male patient with known hypertension, hyperlipidemia, and benign prostatic hyperplasia was admitted in our clinic due to increasing left hip pain for two days. He had undergone open reduction and internal fixation operation with locked plate and screw for left pertrochanteric fracture 18 days earlier in another center (Figure 1a).

On physical examination, swelling, erythema, increased warmth and redness were observed around the skin incision. Hip joint movements were painful and limited. Vascular and neurologic examination was normal in the lower extremity. The Oxford hip score was 3. It was learned that the patient's body temperature had been subfebrile in recent days.

The C-reactive protein (CRP) was 20.4 mg/L, erythrocyte sedimentation rate (ESR) was 53 mm/hour, and Hemoglobin (Hb) was 12.3 gr/L. Pelvis X-ray showed implant insufficiency and loss of reduction (Figure 1b). Due to suspicion of implant related infection joint aspiration was performed under fluoroscopy, which revealed hemopurulent material (Figure 1c).

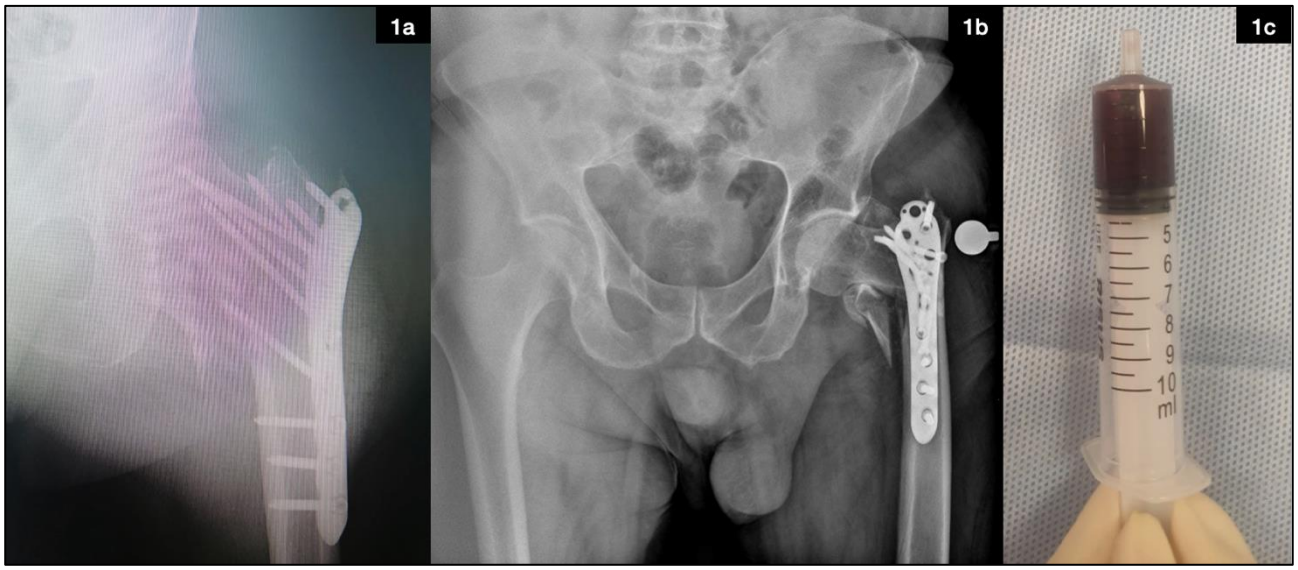

Figure 1. Postoperative X-rays showing plate and screw fixation (1a), implant failure and loss of reduction on Day 18 (1b), and left hip joint aspiration material (1c).

Cell count showed 96.5% polymorphonuclear leukocyte (PMNL) and a white blood cell (WBC) count of 24,223/µL. Oxacillin-resistant Staphylococcus epidermidis was identified in culture.

Additionally, since the patient had a urinary catheter in place since the first surgery, a complete urinalysis and urine culture were also ordered to detect possible urinary tract infection. The urinalysis showed 3+ leukocytes, and the culture revealed growth of Candida parapsilosis. Antibiotherapy was tailored as Rifampicin 300 mg BID, Teicoplanin 800 mg OD, and Fluconazole 200 mg OD. A single-stage revision surgery was planned for treatment.

Previous incision was used and extended for posterior exposure. Plate and screws were loose and removed. Necrotic and infected tissues were removed by performing extensive debridement. The wound was irrigated with Crystalline, Hydrogen peroxide, Chlorhexidine, Betadine, and Serum physiologic. The surgical team was sterilized again, and the surgical equipment was replaced with new ones. Then, an appropriate cementless total hip prosthesis was implanted (Wagner SL revision femoral stem and Trilogy IT acetabular cup, Zimmer Biomed, Warsaw, Indiana, US). One cable was wrapped around the diaphysis to hold the displaced bone fragment in place (Figure 2a).

A hemovac drain was placed. The drain was removed when the amount of drainage decreased to 20 ml/day on the third postoperative day. The patient's general condition was good. There was no fever or discharge at the wound or any other pathological examination finding. On the 7th day, swelling and discharge started at the incision site. Since the hemoglobin values were unstable, repeated ES transfusions were performed.

The next day, as the swelling and discharge increased, the patient was taken back to the operating room for hematoma evacuation. Approximately 1 liter of organized hematoma was evacuated, and two hemovac drains were placed (Figure 2b).

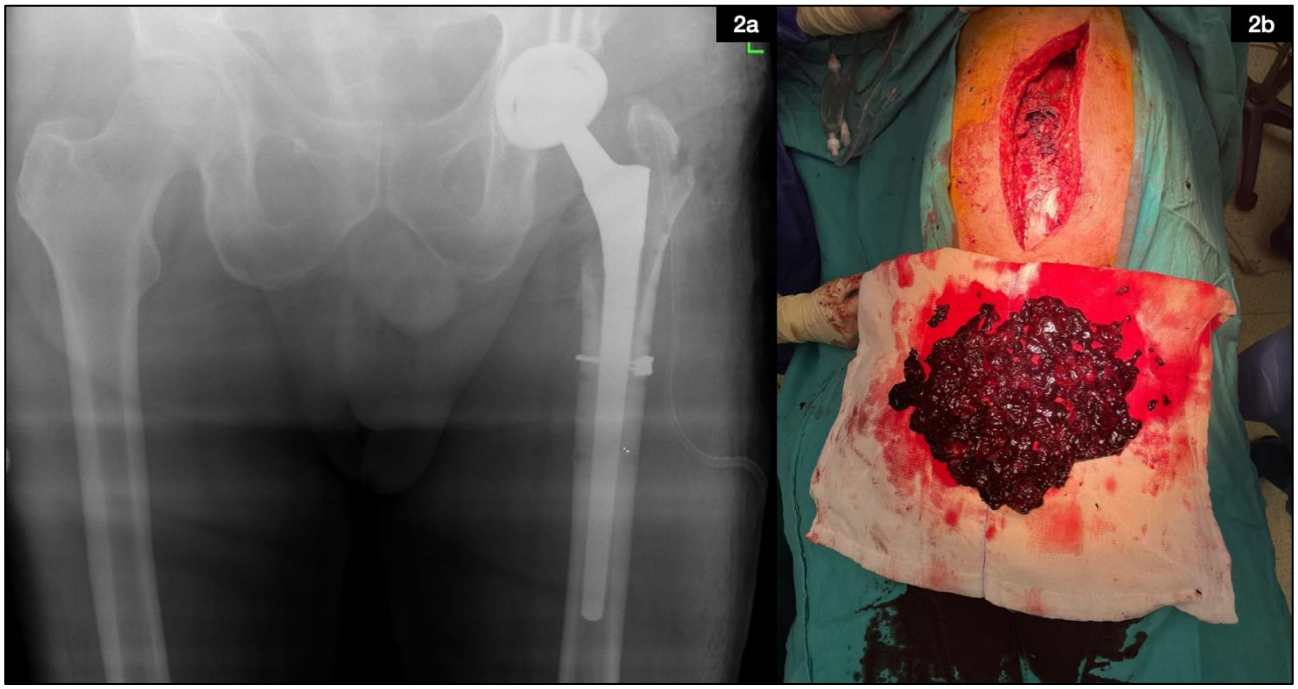

Figure 2. Postoperative imaging and procedures for total hip prosthesis, including X-ray showing a cable at the diaphysis level (2a) and hematoma evacuation after revision total hip arthroplasty (2b).

During postoperative follow-ups, the patient's drainage output remained above 200 ml/day for 6 days. We administered i.v. tranexamic acid 1 gr TID for one month to decrease bleeding. Due to unstable hemoglobin levels, a total of 6 units of packed red blood cells were transfused. As bleeding continued, a CT angiography was performed and showed a pseudoaneurysm at the level of the cable fixation on the femoral diaphysis due to injury to the deep femoral artery branch. Transarterial embolization of the pseudoaneurysm via n-butyl cyanoacrylate glue was performed under angiography by interventional radiology (Figure 3).

After the embolization, the patient's general condition improved, and the bleeding decreased. Hemovac drains were removed on the second day after the embolization. Hemoglobin levels remained stable. However, swelling, wound drainage and fever has started again after 2 days. The CRP levels increased up to 291 mg/dL. Klebsiella Pneumonia growth was seen in a blood culture taken in the intensive care unit. Clinical and

radiological findings indicated an acute postoperative prosthetic joint infection. A second single stage exchange was performed on the 6th day after embolization. Tissue samples were taken for culture. Klebsiella Pneumonia was identified. Antibiotics were tailored as Teicoplanin 400 mg OD, Rifampicin 300 mg BID and Meropenem 1 gr TID according to identified organism. CRP levels returned to normal. Antibiotics were planned to be administered in this regimen intravenously for 2 months and oral with Rifampisin 300 mg BID and Doxycycline 100 mg BID for 6 months after iv therapy was done. The patient's general condition improved, was discharged on the 22nd day after the last surgery.

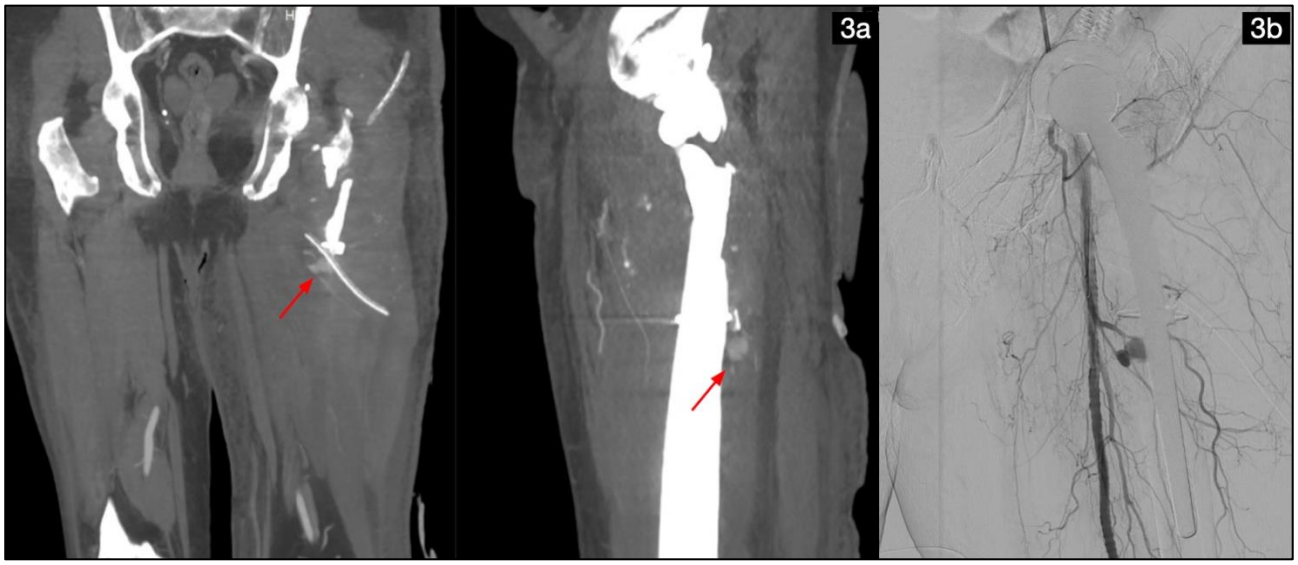

Figure 3. Vascular injury assessment and treatment, including CT angiography showing pseudoaneurysm and arterial injury (red arrows, 3a) and injured artery during embolization (3b).

Discussion

Although vascular injury is a rare complication after THA, it may have serious consequences. In revision surgeries, it is 2.4 times more common than in primary cases (1). The most frequently injured vessels are the superior gluteal artery and deep femoral arteries (4). Vascular injuries are more common around acetabulum compared to femoral region. In this presented case we encountered bleeding of a pseudoaneurysm of deep femoral artery. The deep femoral artery is more susceptible to injury in the proximal femur, as it runs near the diaphysis and between the muscles. The most common causes for vascular injury are retractor compression, direct penetration during acetabular reaming, screw, and PMMA thermal necrosis (1). We were able to find a total of 4 published studies on deep femoral artery pseudoaneurysms in total hip arthroplasty. In one of these (5), the injury was thought to be secondary to intraoperative hip manipulation. In another (6), the authors attributed injury from the osteotome. According to Baker S et al., failure of the revision hardware and subsequent migration of the implants led to damage to the PFA and pseudoaneurysm formation (7). And the last one was thought to be due to either inappropriate and aggressive placement of Hohmann retractors or aggressive exposure of the femur and acetabulum (8). In our case the vessel may be damaged during cable insertion as the vessel is close to the femur.

Clinical suspicion should arise when there is an increasing swelling, a palpable mass, excessive bleeding from the drains and hemodynamic instability. However, in some situations symptoms appear late, and diagnosis may be delayed. Hence close monitoring of patiens regarding bleeding symptoms is paramount to diagnose any vascular injury without delay.

Various radiological imaging methods such as Doppler ultrasound, CT angiography, MR angiography and conventional angiography can be used to diagnose vascular injuries. CT angiography is successful in revealing the vascular anatomy in detail and locating the active bleeding focus, because of its high spatial and temporal resolution. It has also the capability of being able to show the pathology that causes bleeding and help to guide the appropriate treatment.

Treatment methods vary depending on the type and location of the vascular injury. Conservative methods, endovascular intervention with angiography using embolization or stenting, primary repair and excision, are

commonly used treatment options. These options should be evaluated based on the patient's clinical condition, the need for reoperation, and the damage to other anatomical structures. In our case, although we evacuated hematoma we could not find a significant bleeding focus during surgery. In cases of deep-seated bleeding, angiographic treatment methods should be considered. In the presented case, the patient's bleeding stopped and his hemodynamic status stabilized after angiographic embolization.

Bleeding after joint arthroplasty subsequently causes persistent wound drainage and hematoma which serves as a highly nutrient medium for growing microorganisms. Especially if there is a fascial defect, it can lead to prosthetic joint infections (PJI). In a study by Parvizi et al. (9) with 234 primary total knee or hip arthroplasty patients, prolonged wound drainage was present in 31% of PJI cases compared to control group (3%) and hematoma was present in 14% of PJI cases while this rate was 1% in the control group (for both comparison p=0.0001). Galat et al. reported the rate of developing PJI as 10.5% within 2 years in patients undergoing surgery to evacuate hematoma within 30 days after hip arthroplasty, while this rate was 0.8% in patients who did not require hematoma evacuation (10). In our case, hematoma and persistent wound drainage inevitably caused acute postoperative PJI. We proceed with a single stage exchange and antibiotics for treatment. Patient is free of infection and happy with the current clinical condition at the first year follow-up.

Informed Consent: Written consent was obtained from the participant.

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References

1. Troutman DA, Dougherty MJ, Spivack AI, Calligaro KD. Updated strategies to treat acute arterial complications associated with total knee and hip arthroplasty. J Vasc Surg. 2013;58(4):1037-42.
2. Nachbur B, Meyer RP, Verkkala K, Zürcher R. The mechanisms of severe arterial injury in surgery of the hip joint. Clin Orthop Relat Res. 1979;(141):122-33.
3. Shoenfeld NA, Stuchin SA, Pearl R, Haveson S. The management of vascular injuries associated with total hip arthroplasty. J Vasc Surg. 1990;11(4):549-55.
4. Mavrogenis AF, Rossi G, Rimondi E, Ruggieri P, Mercuri M. Embolisation for vascular injuries complicating elective orthopaedic surgery. Eur J Vasc Endovasc Surg. 2011;42(5):676-83.
5. Hall C, Khan WS, Ahmed SI, Sochart DH. A rare case of arterial avulsion presenting with occult blood loss following total hip arthroplasty: a case report. J Med Case Rep. 2009;3:9320.
6. Nozawa M, Irimoto M, Maezawa K, Hirose T, Shitoto K, Kurosawa H. False aneurysm of the profunda femoris artery after total hip arthroplasty. J Arthroplasty. 2000;15(5):671-4.
7. Baker S, Huddleston MK, Goodwin TM, Voskuil R, Sanders C. Left Profunda Femoral Artery Pseudoaneurysm After Revision Total Hip Arthroplasty. Arthroplast Today. 2020;6(4):906-10.
8. Huynh S, Kayssi A, Koo K, Rajan D, Safir O, Forbes TL. Avulsion injury to the profunda femoris artery after total hip arthroplasty. J Vasc Surg. 2016;64(2):494-6.
9. Parvizi J, Ghanem E, Joshi A, Sharkey PF, Hozack WJ, Rothman RH. Does "excessive" anticoagulation predispose to periprosthetic infection? J Arthroplasty. 2007;22(6 Suppl 2):24-8.
10. Galat DD, McGovern SC, Larson DR, Harrington JR, Hanssen AD, Clarke HD. Surgical treatment of early wound complications following primary total knee arthroplasty. J Bone Joint Surg Am. 2009;91(1):48-54.

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Coronary Artery Bypass Surgery: A Narrative Review

Koroner Arter Bypass Cerrahisi: Derleme

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Abstract

Coronary artery bypass surgery has remained the gold standard of coronary revascularization for many years in many patients with coronary artery disease, especially in patients with multivessel coronary artery disease. In this paper, basic information, history and indications related to coronary bypass surgery, as well as preoperative, operative and postoperative approaches and complications are concisely reviewed in the light of current literature and presented to the readers.

Keywords: Coronary Artery Bypass Surgery; Coronary Artery Disease, Review.

&

Öz

Koroner arter bypass cerrahisi, uzun yıllardan beri çoklu damar koroner arter hastaları başta olmak üzere, koroner arter hastalığı olan birçok hastada koroner revaskülarizasyonun altın standardı olma özelliğini devam ettirmektedir. Bu makalede, koroner bypass cerrahisi ile ilişkili temel bilgiler, tarihçe ve endikasyonların yanı sıra preoperatif, operatif ve postoperatif yaklaşımlar ve komplikasyonlar güncel literatür ışığında gözden geçirilerek kısa ama özlü bir şekilde derlendi ve okuyuculara sunuldu.

Anahtar Kelimeler: Koroner Arter Bypass Cerrahisi; Koroner Arter Hastalığı, Derleme

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Introduction

Coronary artery disease (CAD) is a common spectrum of conditions that occurs when blood flow to the myocardium is partially or completely blocked due to narrowing or obstruction of the coronary arteries. CAD is a leading cause of death in developed countries, accounting for approximately one-third of all deaths (1,2). Although it has begun to be seen at younger ages in recent years, the disease primarily affects individuals over the age of 40. Due to the protective effect of estrogen in women, CAD is more frequently observed in men than in women. The disease is commonly seen in men between the ages of 50 and 60, while in women, it most often affects those aged 60 to 70 (3). The main factor contributing to the etiopathogenesis of CAD is "atherosclerosis" (4).

Understanding the risk factors that lead to this disease and taking preventive measures are as important as treating the disease itself. CAD risk factors are divided into two groups: non-modifiable risk factors (genetic predisposition, advanced age, gender) and modifiable risk factors (hypertension, diabetes, hyperlipidemia, smoking, stress, obesity, sedentary lifestyle) (2).

The main treatment methods for CAD include risk modification and medical therapy, percutaneous coronary interventions, and coronary bypass surgery (2,5).

Coronary artery bypass surgery is a surgical treatment aimed at reperfusing coronary arteries that are not adequately perfused due to narrowing or obstruction, thereby restoring their functionality. In this procedure, coronary reperfusion is achieved by bypassing occluded or narrowed coronary arteries through various autologous grafts anastomosed distal to the bypass (6).

History

In the early 1900s, Alexis Carrel performed the first experimental coronary artery bypass surgery on dogs. In 1956, Bailey successfully performed coronary endarterectomy, leading to direct surgical interventions on coronary arteries. In the early 1960s, Sabiston and Garrett published the first case reports of coronary bypass surgeries using the saphenous vein graft (SVG). In 1968, Favaloro reported successful coronary bypass surgeries utilizing the SVG. Prior to the SVG, the internal thoracic artery (ITA) was considered as a graft option. In 1961, Kolesov performed the first coronary bypass surgery using the ITA in Russia. In 1968, Green published the first case series of coronary bypass surgery using the ITA. Following Green's successful outcomes, the ITA became widely used worldwide as a bypass graft (7).

Indications

Individuals being evaluated for coronary artery bypass surgery should be assessed using the Society of Thoracic Surgeons (STS) risk classification. In patients with multi-vessel CAD, tools such as the SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) score can help in evaluating CAD complexity to guide revascularization decisions.

Class I indications for coronary artery bypass surgery are as follows:

1. Stenosis of more than 50% in the left main coronary artery

2. More than 70% stenosis in the proximal left anterior descending (LAD) and proximal circumflex arteries

3. Three-vessel disease in asymptomatic patients or those with mild or stable angina

4. Three-vessel disease with proximal LAD stenosis in patients with impaired left ventricular function

5. Stable angina and one- or two-vessel disease with a large viable myocardial area at high risk

6. Proximal LAD stenosis in patients with an ejection fraction (EF) of less than 50% or more than 70%, with ischemia demonstrated on non-invasive testing (8-10).

Other indications for coronary bypass surgery include:

1. Angina pectoris resistant to medical therapy

2. Persistent ischemia in the presence of non-ST elevation myocardial infarction (NSTEMI) unresponsive to medical treatment

3. The presence of viable but dysfunctional myocardium that can be revascularized in patients with low EF

4. Situations where percutaneous coronary intervention (PCI) is not feasible or has failed, and ischemia and pain continue to threaten a significant area of the myocardium despite medical therapy (8-10).

Preoperative Preparation

Before coronary artery bypass surgery, the patient's medical history should be carefully reviewed for factors that may predispose them to perioperative complications. If possible, these factors should be addressed, and the patient's medical condition should be optimized. Factors that may increase the risk of perioperative complications include recent myocardial infarction (MI), a history of previous heart surgery or chest radiation, conditions predisposing to bleeding (such as anticoagulant or antiplatelet use), renal and/or hepatic insufficiency, carotid artery disease, a history of cerebrovascular disease including transient ischemic attacks (TIA), electrolyte imbalances that may predispose the patient to arrhythmias, infections including urinary tract infections, skin infections, and dental abscesses, as well as respiratory dysfunctions such as chronic obstructive pulmonary disease (COPD) or lung infections.

Routine preoperative evaluations should include a complete blood count, coagulation profile, electrolyte levels, comprehensive biochemical analysis including kidney and liver function tests, chest radiography, electrocardiography (ECG), echocardiography, coronary angiography, and, if possible, carotid Doppler ultrasonography and epiaortic ultrasonography (11,12).

Surgical Approach

The most commonly performed method worldwide and in our country is standard coronary artery bypass surgery using cardiopulmonary bypass (heart-lung machine) and cardioplegic arrest (stopping the heart with solutions called cardioplegia). In this method, following a median sternotomy, arterial cannulation is performed from the ascending aorta and venous cannulation from the right atrial appendage, initiating cardiopulmonary bypass. Then, a cardioplegia solution is administered to stop the heart and temporarily protect the myocardium. During these steps, the bypass grafts are prepared concurrently. The most commonly used grafts are the internal thoracic artery (ITA), saphenous vein graft (SVG), and radial artery (RA). Aorto-coronary bypasses are generally completed by first performing distal coronary anastomoses, followed by proximal aortic anastomoses (13).

Off-pump coronary bypass surgery is performed with using some devices such as Octopus tissue stabilizer on the beating heart without cardiopulmonary bypass support. This surgical technique has been developed in order to avoid detrimental effects of cardiopulmonary bypass such as systemic inflammatory response. Thus, off-pump coronary bypass surgery has been reported to be associated with superior early-term postoperative outcomes to conventional coronary artery bypass surgery using cardiopulmonary bypass (14-16).

Other, less frequently used methods in coronary bypass surgery include beating heart coronary bypass surgery with cardiopulmonary bypass support, and coronary bypass surgery using minimally invasive, endoscopic, and robotic methods, which have gained popularity in recent years (17,18).

Postoperative Management

After the surgery, patients are admitted to the intensive care unit (ICU) and closely monitored with intubated mechanical ventilation support during the critical initial postoperative hours. During these critical hours, continuous monitoring is conducted to track arterial blood pressure, central venous pressure, blood oxygen saturation, heart rate, and rhythm. Blood gases are frequently checked to monitor oxygen, carbon dioxide, and saturation levels, as well as hemoglobin-hematocrit levels, blood pH, lactate, and electrolyte levels. Additionally, drainage output and urine output are carefully monitored. Hemodynamic parameters are maintained as stable as possible, and if necessary, fluid-electrolyte therapies and inotropic support are provided.

Patients who are hemodynamically stable, have minimal drainage, and show adequate wakefulness with normal motor function and neurological assessments are extubated within the first 4-6 hours postoperatively, discontinuing mechanical ventilation support. Patients without significant complications in the following monitoring are mobilized on the first postoperative day and transferred to the ward, where oral medication therapy is initiated (11,15,16).

Complications

Following coronary artery bypass surgery, a range of complications can occur both in the short and long term. These complications may be associated with anesthesia, cardiopulmonary bypass, incisions, and the surgery itself. The most common complications include myocardial dysfunction (perioperative MI, low cardiac output syndrome), cerebrovascular accidents (stroke, transient ischemic attack), bleeding and cardiac tamponade, acute renal failure, infections (pneumonia, mediastinitis, surgical wound infections), and arrhythmias (atrial fibrillation) (19,20).

In the early postoperative period, a temporary and mild decrease in myocardial function is expected due to myocardial edema and ischemia-reperfusion injury. However, additional factors such as incomplete revascularization or graft failure can exacerbate this mild dysfunction. Low cardiac output syndrome, which requires the use of inotropes and/or intra-aortic balloon pumps, occurs in approximately 4-9% of patients, while more severe cases, such as segmental transmural MI, occur in 1-5% of patients (21-23).

Cerebrovascular and neurological adverse events are significant concerns in cardiac surgery. Major events, such as stroke, occur in 1-4% of patients and can increase mortality by up to 10-fold. Embolisms from aortic cannulation and manipulations, microemboli from cardiopulmonary bypass, and low blood flow and hypoperfusion, particularly in individuals with chronic ischemic (relatively) brains (e.g., elderly patients), are responsible for these neurological events (24,25).

Postoperative renal failure is a critical cause of mortality following coronary artery bypass surgery. The incidence of acute renal failure in these patients is approximately 4%, and around 20% of these patients require hemodialysis. The mortality rate for those requiring hemodialysis postoperatively is reported to be about 50% (26).

Atrial fibrillation is also one of the most common complications after coronary artery bypass surgery, occurring in 10-40% of patients, usually on the 2nd or 3rd day post-surgery. Postoperative atrial fibrillation is associated with increased mortality, morbidity, and healthcare costs both in the short and long term (27-30).

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References

1. Okrainec K, Banerjee DK, Eisenberg MJ. Coronary artery disease in the developing world. Am Heart J. 2004;148(1):7-15.
2. Malakar AK, Choudhury D, Halder B, Paul P, Uddin A, Chakraborty S. A review on coronary artery disease, its risk factors, and therapeutics. J Cell Physiol. 2019;234(10):16812-23.
3. Ralapanawa U, Sivakanesan R. Epidemiology and the Magnitude of Coronary Artery Disease and Acute Coronary Syndrome: A Narrative Review. J Epidemiol Glob Health. 2021;11(2):169-77.
4. Sayols-Baixeras S, Lluís-Ganella C, Lucas G, Elosua R. Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants. Appl Clin Genet. 2014;7:15-32.
5. Sulava EF, Johnson JC. Management of Coronary Artery Disease. Surg Clin North Am. 2022;102(3):449-64.
6. Alexander JH, Smith PK. Coronary-Artery Bypass Grafting. N Engl J Med. 2016 May 19;374(20):1954-64.
7. Melly L, Torregrossa G, Lee T, Jansens JL, Puskas JD. Fifty years of coronary artery bypass grafting. J Thorac Dis. 2018;10(3):1960-7.
8. Writing Committee Members; Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: A Report of the American College of

Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(2):e21-e129.
9. Sousa-Uva M, Neumann FJ, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg. 2019;55(1):4-90.
10. Mack MJ, Squiers JJ, Lytle BW, DiMaio JM, Mohr FW. Myocardial Revascularization Surgery: JACC Historical Breakthroughs in Perspective. J Am Coll Cardiol. 2022;78(4):365-83.
11. Çobanoğlu A, İsbir S. Koroner arter bypass cerrahisi. Konu 29, Sayfa: 1-14. Mustafa Paç, Atıf Akçevin, Serap Aykut Aka, Suat Buket, Tayyar Sarıoğlu. Kalp ve Damar Cerrahisi, Medikal Network Nobel Kitabevi, 2013, 2. baskı, 2189. ISBN: 9789755670799
12. Lafçı G, Çağlı K, Özcan F. Koroner arter baypas greft cerrahisi: Güncelleme. Turk Gogus Kalp Dama. 2014;22(1):211-5.
13. Cuminetti G, Bonadei I, Vizzardi E, Sciatti E, Lorusso R. On-Pump Coronary Artery Bypass Graft: The State of the Art. Rev Recent Clin Trials. 2019;14(2):106-15.
14. Dimeling G, Bakaeen L, Khatri J, Bakaeen FG. CABG: When, why, and how? Cleve Clin J Med. 2021;88(5):295-303.
15. Yuksel A, Yolgosteren A, Kan II, Cayir MC, Velioglu Y, Yalcin M, Tok M, Bicer M, Signak IS. A comparison of early clinical outcomes of off-pump and on-pump coronary artery bypass grafting surgery in elderly patients. Acta Chir Belg. 2018;118(2):99-104.
16. Yuksel A, Kan II, Yolgösteren A, Velioğlu Y, Çayır MÇ, Gürbüz O, et al. Are the Early Postoperative Outcomes of Coronary Artery Bypass Grafting Surgery in Elderly Women Worse Compared to Men's? Braz J Cardiovasc Surg. 2017;32(3):191-6.
17. Bonatti J, Wallner S, Crailsheim I, Grabenwöger M, Winkler B. Minimally invasive and robotic coronary artery bypass grafting-a 25-year review. J Thorac Dis. 2021;13(3):1922-44.
18. Sef D, Thet MS, Hashim SA, Kikuchi K. Minimally Invasive Coronary Artery Bypass Grafting for Multivessel Coronary Artery Disease: A Systematic Review. Innovations (Phila). 2024 Sep 12:15569845241265867. Epub ahead of print.
19. Anthony A, Sendelbach S. Postoperative complications of coronary artery bypass grafting surgery. Crit Care Nurs Clin North Am. 2007;19(4):403-15, vi.
20. Hussain SMA, Harky A. Complications of coronary artery bypass grafting. Int J Med Rev. 2019;6(1):1-5.
21. Greaves SC, Rutherford JD, Aranki SF, Cohn LH, Couper GS, Adams DH, Rizzo RJ, Collins JJ Jr, Antman EM. Current incidence and determinants of perioperative myocardial infarction in coronary artery surgery. Am Heart J. 1996 Sep;132(3):572-8.
22. Nicolas J, Soriano K, Salter B, Gross CR, Oloomi M, Dangas G. Myocardial infarction after cardiac surgery: When to intervene? J Thorac Cardiovasc Surg. 2023;165(3):1195-201.
23. Gaudino M, Jaffe AS, Milojevic M, Sandoval Y, Devereaux PJ, Thygesen K, Myers PO, Kluin J. Great debate: myocardial infarction after cardiac surgery must be redefined. Eur Heart J. 2024;45(39):4170-7.
24. LaPiano JB, Arnott SM, Napolitano MA, Holleran TJ, Sparks AD, Antevil JL, Trachiotis GD. Risk factors for cerebrovascular accident after isolated coronary artery bypass grafting in Veterans. J Card Surg. 2022;37(10):3084-90.
25. Ferrante MS, Pisano C, Van Rothem J, Ruvolo G, Abouliatim I. Cerebrovascular events after cardiovascular surgery: diagnosis, management and prevention strategies. Kardiochir Torakochirurgia Pol. 2023;20(2):118-22.
26. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. Nat Rev Nephrol. 2017;13(11):697-711.
27. Yuksel A, Velioglu Y, Tecimer ME, Kan II, Bicer M, Gurbuz O, et al. Is there any relationship of postoperative atrial fibrillation with the use of blood products and postoperative hemoglobin levels in patients undergoing coronary artery bypass grafting? Medicine Science. 2019;8(1):16-20.
28. Yuksel A, Velioglu Y, Atasoy MS, Muduroglu A, Gurbuz O, Aldemir M, et al. Multi-inflammatory index as a novel predictor of new-onset atrial fibrillation after off-pump coronary artery bypass grafting. Kardiol Pol. 2024;82(7-8):733-40.
29. Velioglu Y, Yuksel A. Predictors of Postoperative Atrial Fibrillation after Beating-Heart Coronary Artery Bypass Surgery: Is Cardiopulmonary Bypass a Risk Factor? Acta Cardiol Sin. 2019;35(5):468-75.

30. Topal D, Korkmaz UTK, Velioglu Y, Yuksel A, Donmez I, Uçaroğlu ER, Kayis SA. Systemic immune-inflammation index as a novel predictor of atrial fibrillation after off-pump coronary artery bypass grafting. Rev Assoc Med Bras (1992). 2022;68(9):1240-6.

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