Volume 46 ◦ Issue 1 ◦ March 2024

Cumhuriyet Medical Journal

Official Journal of Sivas Cumhuriyet University
Faculty of Medicine

e-ISSN: 1305-0028

cmj.cumhuriyet.edu.tr

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Cumhuriyet Medical Journal

Official Journal of the Sivas Cumhuriyet University Faculty of Medicine

Volume 46 Issue 1 March 2024

CMJ.2024;46(1):1-7
DOI: 10.7197/cmj.1411030

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Chiari Malformations: Historical Background, Anatomical Forms and Treatment Approaches

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Review

History

Received: 27/12/2023
Accepted: 25/02/2024

ABSTRACT

Chiari malformations (CM) refer to a series of anomalies characterized by the descent of cerebellar tonsils into the cervical spinal canal. These malformations can be associated with abnormalities such as syringomyelia, hydrocephalus, spina bifida, and scoliosis. Additionally, cranio-cervical junction anomalies, endocrinopathies, craniosynostosis, and syndromic disorders are also linked to CM. The treatment of CM is surgical, and there is no known medical therapy. Patients diagnosed with CM are typically advised to undergo surgical treatment or follow-up. Although surgical intervention is supported in the literature, debates exist regarding which procedure is most suitable and when surgery should be performed. In this article, we will examine the historical background of CM, its anatomical forms, pathophysiology, clinical presentation, relationship with other diseases, and diagnostic procedures in the light of the literature.

Keywords: Arnold Chiari Malformation, history, etiology, diagnosis, treatment

Chiari Malformasyonları: Tarihsel Arka Plan, Anatomik Formlar ve Tedavi Yaklaşımları

Derleme

Süreç

Geliş: 27/12/2023
Kabul: 25/02/2024

ÖZET

Chiari malformasyonları (CM), serebellar tonsillerin servikal spinal kanala inmesiyle karakterize edilen bir dizi anomaliyi ifade eder. Bu malformasyonlar, siringomiyeli, hidrosefali, spina bifida ve skolyoz gibi anormalliklerle ilişkilendirilebilir. Ayrıca, kraniyoservikal bileşke anomalileri, endokrinopatiler, kranyosinostoz ve sendromik bozukluklar da CM ile bağlantılıdır. CM'nin tedavisi cerrahidir ve bilinen bir tıbbi tedavisi yoktur. CM tanısı alan hastalara genellikle cerrahi tedavi veya takip önerilir. Cerrahi müdahalenin literatürde desteklendiği görülse de hangi prosedürün en uygun olduğu ve ameliyatın ne zaman yapılması gerektiği konusunda tartışmalar bulunmaktadır. Bu makalede, CM'nin tarihsel arka planı, anatomik formları, patofizyolojisi, klinik sunumu, diğer hastalıklarla ilişkisi ve literatür ışığında tanı prosedürleri incelenecektir.

Anahtar Kelimeler: Arnold Chiari Malformasyonu, Öykü, Etiyoloji, Tanı, Tedavi

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How to Cite: Bulut Z. Chiari Malformations: Historical Background, Anatomical Forms and Treatment Approaches. Cumhuriyet Medical Journal. 2024;46(1):1-6.

Introduction

Chiari Malformation is a group of conditions characterized by the descending part of the posterior brain structures through the foramen magnum into the cervical spinal cord.[1] This condition was first described by J. Cleland in 1883. In 1894, German pathologist Julius A. Arnold identified and published a case of posterior brain herniation in a myelodysplastic patient in Heidelberg. Subsequently, Hans von Chiari classified these herniations into grades, creating a classification system. Chiari initially described three types of malformations and later added a fourth type, which does not involve herniation of the posterior fossa structures. This classification was completed in 1896 by Hans Chiari, leading to the well-known classic four types of Chiari Malformation.[2] Over the years, different variations of Chiari Malformation have been identified. These include Chiari Malformation Type 0 (Chiari-like malformation), Type 1.5, Type V, and Complex Chiari.[3]

A significant milestone in the surgical treatment of Chiari Malformation was set in 1932 by Cornelis Joachimus van Houweninge Graftdijk, a Dutch professor of neurosurgery. Graftdijk performed the first Chiari operation, removing the suboccipital bone and excising the cerebellar tonsils. Some losses were also reported in these early surgical interventions.[4]

In 1941, studies conducted by List,[5] and in the same year by Adams, Schatzki, and Scoville[6] first demonstrated obstruction at the level of the foramen magnum using myelography, marking a significant advancement in the diagnosis of Chiari disease. With the widespread adoption of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) technologies, the diagnosis of Chiari Malformation has become even more accessible.

Physiopathogenesis

Several theories have been proposed to understand the etiology of Chiari Malformation (CM), but none have been sufficient to fully explain this complex condition on their own. The origin of CM, whether as a continuation of an embryological anomaly or as a result of a pathology developed later, remains unclear. The following are the main theories in this regard:

Traction Theory: According to this theory, conditions located caudally, such as meningomyelocele, cause the spinal cord to adhere to surrounding tissues and pull the hindbrain structures downward. This process impedes the upward migration of the tonsils during the 9th week of intrauterine life.[7] However, this theory does not explain the upward movement of the cerebellum towards the tentorium.[8]

Developmental Arrest Theory: This theory posits that dysgenetic development in the brainstem is the primary pathology. A developmental arrest during embryogenesis prevents the formation of the pontine flexure, leading to the elongation of the brainstem and the descent of posterior fossa structures into the spinal canal.[9]

Hydrodynamic Theory: Proposed by Gardner in 1950, this theory suggests that pulsatile forces in the supratentorial ventricular region's choroid plexus and the area of the 4th ventricle differentially affect brain development. When supratentorial forces are dominant, the tentorium is pushed caudally, causing compression of posterior fossa structures.10 If the pulsatile forces of the 4th ventricle dominate, it results in the development of Dandy-Walker anomaly.[11]

Overgrowth Theory: In 1932, van Houweninge Graftdijk proposed that the vertebral column grows faster than the spinal cord, leading to the migration of infratentorial structures towards the occipital foramen.[12]

Small Posterior Fossa Theory: This theory explains that a primary paraxial mesodermal insufficiency results in the bony structures of the posterior fossa being smaller than normal, leading to the herniation of the brainstem and cerebellum into the cervical canal.[13]

Neurodystrophic (Distrophic) Theory: Described by Osaka and colleagues in 1978, this theory suggests that developmental disorders of the lumbar spinal cord, similar to conditions like meningomyelocele, lead to cerebrospinal fluid (CSF) leakage. This leakage causes a decrease in CSF pressure, which in turn allows the cerebellar tonsils to sag into the upper cervical canal. However, this theory does not explain Type 1 Chiari Malformation (CM1).[13,14]

These theories, while contributing significantly to the understanding of the complex nature and etiology of Chiari Malformation, each explain only specific aspects of the disease. A comprehensive understanding requires integrating these theories.

Diagnosis

There are several imaging and testing methods used for the diagnosis of Chiari Malformation (CM), playing a critical role in its accurate identification and treatment.

Cervical Magnetic Resonance Imaging (MRI): MRI is the most important imaging method for diagnosing Chiari Malformation.[15] Typically, a descent of the cerebellar tonsils more than 5 mm below the foramen magnum is considered pathological. However, some sources also consider a herniation of 0 or 2 mm as pathological.[16]

Computed Tomography (CT) and Direct Radiographs: These imaging methods are preferred in patients suspected of having cranio-cervical bone anomalies. If MRI is contraindicated, metrizamide-enhanced CT imaging can be used as an alternative option.[8,17]

Cine-Mr Imaging: This is used to assess cerebrospinal fluid (CSF) circulation in CM1 patients with syringomyelia. Cine-MR imaging can reveal that while CSF flow in the anterior region is normal in Chiari patients, there is reduced or absent flow in the posterior region. Four-dimensional MRI flow techniques have shown the potential to reveal complex flow characteristics through qualitative and quantitative flow analysis.[15,18,19]

Ultrasonography (Usg): Used in infants for the diagnosis of Chiari and the detection of syringomyelia.

Routine prenatal ultrasonographic examinations can identify developmental anomalies such as Chiari malformation and spinal dysraphism early on.[18,19]

Neurophysiological Tests: These tests can assess compressions of the posterior fossa and spinal cord. However, it has been reported that neurophysiological tests are not always functional in children.[20]

These imaging and testing methods are vital for the accurate diagnosis and appropriate treatment planning of Chiari Malformation. Each method illuminates different aspects of the disease, aiding in the best possible treatment of patients.

Chiari Malformation Types and Clinical Findings

Chiari Malformation is divided into various types, and each type has its own unique features and treatment needs.

Chiari Malformation Type 1 Features and Clinical Findings

Definition and Frequency: CM1 is characterized by the herniation of the cerebellar tonsils into the cervical canal by 5 mm or more. It usually occurs sporadically, and genetic transmission is rare.[21] It is more common in women and most often manifests between the ages of 30 and 50.[21,22] Cranial and cervical pathologies may also accompany CM1. CM1 is found in about 0.9% of the adult population and 0.6% of the pediatric population, with one-third of patients exhibiting clinical symptoms.[23]

Clinical Symptoms: CM1 patients may present with symptoms ranging from simple head and neck pain and numbness in the extremities to more serious complaints such as difficulty swallowing and sudden respiratory arrest.[24] The level of cerebellar tonsil herniation can influence the severity and variety of clinical findings, though this is not always the case.[25] Clinical symptoms may occur due to compression of the brain stem, spinal cord, lower cranial nerves, and cerebellum caused by volume loss in the posterior fossa and the descent of the cerebellar tonsils.[26,27]

Classification of Findings: Milhorat and colleagues have classified the clinical findings of CM1 into five main groups: Suboccipital headache, ocular disorders, neuro-otological disorders, brain stem-related clinical findings, and spinal cord findings.[28]

Pain: Headache is the most common complaint in 80-90% of CM1 patients.[22] Pain, particularly concentrated in the occipital and upper cervical region and triggered by Valsalva maneuvers, is typical.[22]

Cerebellar Findings: Approximately 30-52% of CM1 patients exhibit cerebellar signs. These include balance disturbances, gait, and coordination problems, dysmetria, dysdiadochokinesia, dysarthria, ataxia, and nystagmus.[29,30]

Lower Cranial Nerve and Brainstem Involvements: These symptoms are less common and may include voice thickening, dysphagia, facial sensory deficits, and sleep apnea.[29-31]

Spinal Cord Findings: The common occurrence of clinical findings related to the spinal cord (63%) can be explained by the frequent radiological association of CM1 with syringomyelia (30-70%). Motor and sensory loss are common.[26,27]

Ophthalmological and Otological Findings: Symptoms such as blurred vision, nystagmus, diplopia, and tinnitus have also been reported among CM1 patients.[30]

Cognitive Complaints and Mood Disorders: CM1 patients may experience psychiatric disorders such as distractibility, depression, and general lethargy. Although the pathogenesis of these complaints, which may benefit from surgery, is not fully explained, they have been suggested to possibly be a form of "cerebellar seizure".[32]

Systemic Problems: Systemic symptoms like chest pain, shortness of breath, hiccups, postural hypotension, and syncopal attacks have also been reported.[26,27,31]

Other Types of Chiari Malformation

Chiari Type II: Commonly seen in children and often associated with spinal dysraphism. It is characterized by the descent of the brainstem and posterior fossa structures into the cervical canal. Also known as Arnold-Chiari syndrome.[21,33]

Chiari Type III: The rarest type, characterized by the herniation of the cerebellum and brainstem into an encephalocele sac. It has the worst prognosis.[21]

Chiari Type IV: Defined by severe cerebellar aplasia or hypoplasia. The posterior fossa volume is reduced, but there is no descent into the spinal canal. Despite poor radiological images, patients exhibit mild to moderate neurological deficits. It does not cause significant symptoms and does not require treatment.[9]

Chiari Type V: Characterized by cerebellar agenesis and herniation of the occipital lobes into the cervical canal.[34]

Chiari Type 0: Characterized by the presence of syringomyelia without tonsillar herniation and improvement of clinical symptoms following posterior fossa decompression.[16]

Chiari Type 1.5: Defined as a type of Chiari where, in addition to the herniation of cerebellar tonsils, as seen in Chiari Type 2, the brainstem, vermis, and IV ventricle are also involved, but without accompanying spinal dysraphism. Similar to CM1, it is observed in the adult age group.[33]

The term "Complex Chiari," as defined by Brockmeyer in 2011, refers to a more complex condition seen in patients with Chiari Malformation Type 1 (CM 1). This condition encompasses cases of CM 1 accompanied by one or more radiographic findings such as brainstem herniation, retroflexed odontoid, basilar invagination, abnormal clivus-cervical angle, occipitalization of the atlas, syringomyelia, or scoliosis. Brockmeyer noted that Posterior Fossa Decompression (PFD) alone may not be sufficient in these complex CM 1 cases. Additional treatments such as odontoid resection and occipitocervical fusion may be necessary.[3] This approach has been supported in subsequent studies.[35]

Treatment methods vary based on the patient's symptoms and the type of malformation. Surgical intervention is preferred, especially in CM1 cases with significant symptoms and accompanying syringomyelia.

Pathologies Accompanying CM1

Syringomyelia is a condition characterized by the formation of longitudinal cystic cavities in the spinal cord, leading to compression and various neurological issues. Though more common in adults, it can also occur in children and is often associated with anomalies of the spine and cervicomedullary junction. Known by various names such as syrinx, hydromyelia, syringohydromyelia, and intramedullary cyst, syringomyelia most frequently appears in the lower cervical region but can occur anywhere along the spinal cord.[37] This condition is predominantly congenital and shows more clinical manifestations between the ages of 25-40, though it is rarer in children, with distal syringomyelia being more common in this age group. Slightly more prevalent in males, syringomyelia is a common pathology accompanying CM1, found in 50-80% of CM1 patients, typically beginning in the cervical region.[22,37] Syringomyelia is a slowly progressing disease with variable symptoms.[36] In adults, syringomyelia can present various clinical symptoms, while in children, spinal anomalies and scoliosis are significant findings.[37,38]

Scoliosis is a common condition in patients with CM1 and syringomyelia. About 15-30% of CM1 patients have scoliosis.[22,30]

Hydrocephalus is frequently seen in CM1 patients, with an incidence of approximately 7-10% at diagnosis.[37,39] Hydrocephalus is a significant complication in CM1 patients and can be treated with shunt surgeries or endoscopic third ventriculostomy (ETV).[37,38]

Posterior Fossa Arachnoid Cysts have been associated with CM1 and syringomyelia, and surgical intervention may be required in these cases. These surgeries aim to increase cerebrospinal fluid (CSF) flow and relieve congestion at the level of the foramen magnum.[40]

Craniosynostosis was first reported in CM1 cases by Saldino and colleagues.[41] It occurs due to the premature closure of skull bones and has been observed that surgeries for craniosynostosis in CM1 patients can correct tonsillar herniation and clinical symptoms.[41]

Hyperostosis, or excessive thickening of bones, particularly when occurring in the posterior fossa region, can lead to a reduction in the volume of this area and contribute to the herniation of the cerebellar tonsils. There is a possibility of CM1 occurring in Paget's disease.[42]

Osteopetrosis, typically seen in late childhood or adulthood, is characterized by thickening of the skull and neurological symptoms due to the narrowing of cranial foramina. It has been suggested that excessive thickening of the posterior fossa bones in osteopetrosis can lead to CM1.[43]

Bone Mineral Deficiency, especially in familial vitamin D-resistant rickets, indicates that CM1 can commonly occur in association with thickening of the posterior fossa bones. Low serum phosphate levels can trigger bone growth and thickening, leading to the narrowing of the foramen magnum and the development of CM1.[44]

Endocrine Disorders can be associated with CM1. In cases of growth hormone deficiency, CM1 has been reported in 5-20% of patients. Acromegaly, causing excessive bone growth and thickening of the posterior fossa bones, can contribute to the development of CM1.[45] Similarly, achondroplasia can lead to a reduction in the volume of the posterior fossa and the development of CM1.[42,45]

Basilar Invagination, one of the most common craniocervical bone anomalies, is defined by the odontoid process extending more than 5 mm above the Chamberlain line.[46] A study reported a 14.2% association with CM1.[46] In cases of CM1 combined with basilar invagination, performing only foramen magnum decompression (FMD) may lead to instability or lack of improvement in patients.[47] In such cases, if craniovertebral instability is present, stabilization in conjunction with decompression is recommended.[47] Another approach can be anterior dens resection followed by FMD and posterior stabilization.[48]

A study reported significant improvement in patients with CM1 and basilar invagination after FMD and stabilization.[47] For patients with basilar invagination without anterior compression, FMD alone may suffice.[46]

Atlantoaxial Dislocation (AAD) can occur in conjunction with CM1. AAD should be considered in CM1 patients who exhibit symptoms such as neck pain that worsens with movement, advanced motor deficit, spasticity, posterior column signs, and sphincter disturbances.[49]

Atlas Occipitalization is frequently encountered in CM1, especially in cases with basilar invagination.[49] This condition involves an abnormal fusion between the atlas and the occipital bone. It has been reported that brainstem compression symptoms are more common in patients with CM1 and atlas occipitalization than in typical CM1 patients.[50]

Klippel-Feil Syndrome is a condition characterized by the abnormal fusion of spinal bones and is associated with CM1 in about 3.3-5% of cases.[48] Due to the frequent co-occurrence of Klippel-Feil Syndrome and CM1, it is thought that these conditions might share a common genetic disorder.[51] Klippel-Feil Syndrome primarily occurs in the upper cervical region and often presents with Atlantoaxial Dislocation (AAD).[49]

Neurofibromatosis Type 1 is an autosomal dominant neurocutaneous syndrome characterized by various skin lesions, neurological findings, and tumor formation. It is one of the most commonly associated neurocutaneous syndromes with CM1. CM1 can be found in approximately 5% of patients with neurofibromatosis type 1.[52] It is believed that this syndrome contributes to the development of CM1 by causing a halt in the development of the posterior fossa.[51] A connection between the SUZ12 gene, which codes for the SUZ12 protein, and NF1 and CM1 has been reported, and this gene is located on chromosome 17.[51]

Rare diseases that are associated with Chiari syndrome include hereditary connective tissue disorders, bone dysplasias, transverse sinus stenosis, spina bifida, intracranial hypotension, Klippel-Trenaunay syndrome,

Morning Glory disk anomaly, dehiscence of the semicircular canals, Rubinstein-Taybi syndrome, and Gorham's disease of the skull base.

These associations underscore the complexity of Chiari syndrome and the need for comprehensive evaluations in patients, as they may present with a spectrum of related conditions that impact diagnosis and treatment strategies.

Treatment

Treatment and follow-up of CM1 remain subjects of various debates. Primarily, if the patient has other conditions like hydrocephalus or Craniospinal Junction Abnormalities Classification (CSJAC), it is recommended to address these emergencies or conditions first before focusing on correcting CM1. Approximately 7-10% of CM1 patients are found to have hydrocephalus.[39] In a study by Klekamp, only 9.5% of 644 CM1 patients were followed up without surgery, indicating that most CM1 patients require surgical intervention.[37]

The natural course of Syringomyelia (SM) associated with CM1 is not fully understood. Nishizawa and colleagues followed 9 patients without significant clinical symptoms and neurological findings for 11 years, reporting that only one required surgery due to clinical deterioration.[38] In untreated cases of SM, irreversible cervical myelopathy can develop in the cord.[53]

The consensus is to recommend surgical intervention for all CM1 cases accompanied by a syrinx. However, studies have observed that in asymptomatic cases with a syrinx, many patients did not show growth in their syrinx cavities when followed without surgery.[53,54] Therefore, asymptomatic CM1 patients, even with a syrinx cavity, can be managed without surgery. However, surgical treatment is commonly preferred in patients with progressive scoliosis or clinical symptoms.[55]

In patients without a syrinx cavity, if there is minimal tonsillar herniation and non-life-limiting headaches, monitoring is advised. However, surgical treatment is recommended in cases of life-limiting headaches, respiratory distress, or cranial nerve involvement.[30] This underscores the need for individual assessment of each CM1 patient based on their unique condition and symptoms.

The standard surgical treatment for Chiari Malformation Type 1 is known as Foramen Magnum Decompression (FMD). This procedure aims to relieve pressure on the brainstem and normalize the flow of cerebrospinal fluid (CSF). FMD involves removing part of the margin of the foramen magnum and often includes the removal of the C1 lamina. If the tonsillar herniation extends down to the C2 level, the upper part of the C2 lamina may also need to be removed.[32]

Foramen Magnum Decompression (FMD) can be performed using two main methods:

Foramen Magnum Decompression and C1 Laminectomy with Vertical Dural Incisions: This method usually preserves the integrity of the dura mater. Vertical incisions on the dura are made to relieve the pressure without opening it.[22,56]

FMD and C1 Laminectomy with Dural Opening and Duraplasty: This method provides a more extensive decompression by opening the dura mater and enlarging it with Duraplasty. It is used to expand the dura mater for more comprehensive decompression.[22,56]

Recently, new treatment approaches have been suggested for CM and syringomyelia, especially when associated with atlantoaxial instability. Notably, Goel has emphasized the necessity of C1-C2 stabilization in the treatment of CM and syringomyelia.[57] This approach could be a significant alternative, particularly for patients with instability in the atlantoaxial joint. Such innovative treatment methods offer new perspectives in the treatment of CM1 and syringomyelia, playing a crucial role in providing more specific interventions tailored to the patient's conditions.[57-58]

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CMJ.2024;46(1): 8-12
DOI: 10.7197/cmj.1369992

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Complete Blood Count in Multiple Sclerosis

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Review

History

Received: 02/10/2023
Accepted: 08/03/2024

ABSTRACT

Multiple sclerosis (MS) is a chronic disease that affects the central nervous system in primarily young adults. Although the exact etiology of MS is unknown, autoimmune mechanisms are thought to play a crucial role, especially with CD4+ T cells involved in the immune response. Inflammatory reactions involving T cells and macrophages are commonly observed in MS lesions. B lymphocytes, plasma cells, and antibodies also contribute to MS pathogenesis. Neutrophils, lymphocytes, monocytes, and platelets, key immune system components, play roles in inflammatory processes, but their association with MS prognosis remains inconclusive. Due to its heterogeneous nature, clinical manifestations of MS vary depending on the location of the affected central nervous system. While several potential biomarkers have been identified for MS diagnosis and monitoring, none have been universally accepted. Studies have examined complete blood count parameters in MS patients, including erythrocyte, platelet, and leukocyte populations. Changes in these parameters have been observed in MS patients compared to healthy controls and may be related to disease prognosis. For example, increased erythrocyte fragility and altered hemoglobin levels have been reported in MS patients. Leukocyte counts and ratios, such as the neutrophil/lymphocyte ratio, have shown associations with disease severity. Platelet activation and interaction with immune cells have also been implicated in MS pathophysiology. Nevertheless, further research is needed to fully understand the role of complete blood count parameters in MS. Identifying reliable biomarkers for early diagnosis and prognosis prediction would greatly enhance MS management. Moreover, these benefits could lead to substantial improvements in achieving complete recovery of patients, surpassing the focus on current symptomatic treatments.

Keywords: Complete Blood Count, Multiple Sclerosis, Immune System

Multipl Sklerozda Tam Kan Sayımı

Derleme

Süreç

Geliş: 02/10/2023
Kabul: 08/03/2024

ÖZET

Multipl skleroz (MS), öncelikle genç yetişkinlerde görülen ve merkezi sinir sistemini etkileyen kronik bir hastalıktır. MS'nin etiyolojisi tam olarak bilinmemekle birlikte, immün yanıtta önemli görevleri olan CD4+ T hücrelerini içeren otoimmün mekanizmaların rol oynadığı düşünülmektedir. T hücreleri ve makrofajların dahil olduğu inflamatuar reaksiyonlar, MS lezyonlarında yaygın olarak görülür. B lenfositleri, plazma hücreleri ve antikorlar da MS patogenezine katkıda bulunur. Temel bağışıklık sistemi bileşenleri olan nötrofiller, lenfositler ve monositlere ek olarak trombositler de inflamatuar süreçlerde rol oynar, ancak bu hücrelerin MS prognozu ile ilişkileri kesin değildir. Heterojen doğası nedeniyle, MS'nin klinik belirtileri etkilenen merkezi sinir sisteminin konumuna bağlı olarak değişir. MS tanı ve takibi için birkaç potansiyel biyobelirteç tanımlanmış olsa da bunların hiçbiri evrensel olarak kabul edilmemiştir. Çalışmalar, MS hastalarında eritrosit, trombosit ve lökosit popülasyonları dahil olmak üzere tam kan sayımı parametrelerini incelemiştir. MS hastalarında sağlıklı kontrollere kıyasla kan sayımı testlerinde gözlenen değişiklikler, hastalık prognozu ile ilişkili olabilir. Örneğin, MS hastalarında eritrosit frajilitesinde artış ve hemoglobin seviyelerinde değişiklikler bildirilmiştir. Lökosit sayıları ve nötrofil/lenfosit oranının hastalık şiddeti ile ilişkili olduğu gösterilmiştir. Trombosit aktivasyonu ve immün hücrelerle etkileşim de MS patofizyolojisine katkıda bulunmaktadır. Bununla birlikte, MS'de tam kan sayımı parametrelerinin rolü üzerine kesin bilgiler sağlamak için bu alandaki çalışmaların genişletilmesine ihtiyaç vardır. Erken tanı ve prognoz tahmini için güvenilir biyobelirteçlerin tanımlanması, MS hastalarını yönetimini büyük ölçüde geliştirecektir. Dahası, bu faydalar, mevcut semptomatik tedavilere odaklanmanın ötesine geçerek hastaların iyileşmesini sağlamada önemli gelişmelere yol açabilir.

Anahtar Kelimeler: Tam Kan Sayımı, Multipl Skleroz, Bağışıklık Sistemi

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How to Cite: Bolat S, Kablan D. Complete Blood Count in Multiple Sclerosis. Cumhuriyet Medical Journal. 2024;46(1):8-12.

Introduction

Multiple sclerosis (MS) is a chronic disease characterized by diffuse demyelinating lesions in the central nervous system (CNS), often affecting young adults. Although the underlying exact mechanisms is unknown, autoimmunity are thought to play a role in its etiopathogenesis.[1] MS is a highly heterogeneous disease and patients may present with various clinical manifestations including motor and sensory loss and autonomic disorders depending on the area of the central nervous system affected.[2] Clinical findings vary according to the localization and extent of demyelinating lesions.[3] In general, there are three types of MS: Relapsing-remitting multiple sclerosis (RRMS), Primary Progressive Multiple Sclerosis (PPMS) and Secondary Progressive Multiple Sclerosis (SPMS).[3,4] There is no proven curative treatment for MS yet, so current treatments are of a temporary nature, such as reducing the frequency of attacks and alleviating symptoms.[5] Although many biomarkers that are thought to be used in diagnosis and follow-up have been defined, a reliable and generally accepted marker has not yet been identified in the studies conducted to date.[6,7]

Immune system is classified as the innate and acquired immune system. The components of the innate immunity respond very quickly to changes in homeostasis, whereas the acquired immune response takes time and is much more specific.[8] The cellular components of innate immunity are natural killer (NK) cells, macrophages, monocytes, and neutrophils. T and B lymphocytes, which are the main cellular components of acquired immunity, specifically recognize, proliferate and activate against a pathogen.[9] The importance of the innate and acquired immune system in the MS pathogenesis is indisputable. $CD4^+$ T cells take the first place in the immune response in MS.[10] T lymphocytes produce immune activation against other myelin antigens, especially myelin basic protein (MBP).

Although pathological examination of MS lesions has revealed different mechanisms in the development of demyelination, inflammatory reactions caused by T lymphocytes and macrophages have been found in the majority of lesions.[11] In addition, B lymphocytes, plasma cells, and antibodies are also thought to play a role in the pathogenesis of MS. It is also well known that neutrophils, lymphocytes, monocytes, and platelets, which are important elements of the immune system, are effective in the control of systemic inflammation and undergo changes in inflammation processes. Although studies conducted with MS patients, have suggested that neutrophil, lymphocyte, platelet, and monocyte counts may be associated with prognosis, no definitive conclusion has been reached.[6,7]

In this review, we evaluated the findings of some studies in which complete blood count parameters (neutrophil, lymphocyte, erythrocyte, platelet, and monocyte populations) were examined in MS patients.

Complete Blood Count

The complete blood count (CBC) or hemogram, is a test that allows us to obtain information about the number of cells in the blood, their percentages, and some characteristics of these cells. The comparison of measurement methods used by different analyzers is given in Table 1.

In a complete blood count, erythrocyte, platelet, and leukocyte counts and indices are determined by direct measurement or calculation. One of the measurement methods is flow cytometry. It is a technology used to measure multiple properties of a single cell (or bacteria etc.) simultaneously at high speed. Flow cytometry consists of three systems: a channel system, an optical system, and an electrical system, which detects light and fluorescence scattered from cells. This provides information about the size, cell membrane, cytoplasm, and nucleus of leukocytes and subgroups.[12] These data help us to learn about many inflammatory and non-inflammatory changes. While optical methods are used for leukocyte counts, erythrocytes and platelets are counted by impedance method.

Erythrocytes count, mean corpuscular volume (MCV), hematocrit (HCT), hemoglobin (HB), mean hemoglobin concentration (MCH), red blood cell distribution (RDW), and nucleated red blood cells (NRBC) data provide information about erythropoiesis function. Platelet (PLT), mean platelet volumes (MPV), platelet width (PDW), and plateletcrit (PCT) values give us information about primary hemostasis. Reticulocyte count (RET) is a very valuable parameter in the evaluation of bone marrow response, especially for the differential diagnosis of anemia when MCV is normal. Neutrophils, eosinophils, basophils, monocytes, and lymphocytes play an important role in the diagnosis and follow-up of various inflammatory diseases.[13,14] Today's advanced devices can also count erythroblasts and immature granulocytes (IG). IG increases in sepsis and bacterial infections.[15]

Red Blood Cell (RBC)

Erythrocytes (or red blood cells) are disk-shaped, non-nucleated cells measured in the complete blood count. Their most important function is to transport oxygen and carbon dioxide between the tissues and the lungs. Hemoglobin is a tetrameric protein that contains two different globulin chains and fills almost the entire cell content. Through hemoglobin, erythrocytes bind oxygen in the lungs and deliver to the tissues, take carbon dioxide from the tissues and bring it back to the lungs. Reticulocytes are the nucleated intermediate cells observed during the maturation of erythrocytes.[16,17]

Recent studies and clinical observations show that hemoglobin and RBCs may play an important role in the pathogenesis of MS. It is stated that MS patients have higher erythrocyte fragility which leads to increased free Hb and damages the blood-brain barrier and myelin basic protein. It is also thought that increased iron levels will trigger inflammatory events.[18] In a study of 73 MS patients and 38 healthy controls, RBC osmotic fragility was reported to be

Table 1. Blood count parameters measurement methods of different devices.[12]

Parameter	Beckman Coulter UniCel DxH 800	Sysmex XN Series	Abbott CELL-DYN Sapphire	ADVIA 2120i	Mindray BC Series
WBC	Impedance	Fluorescent dye light scatter	Light scatter	Light scatter	Fluorescent dye light scatter
RBC	Impedance	Impedance	Impedance	Laser light scatter	Impedance
HGB	Cyanhemoglobin 525 nm	Sodium lauryl sulfate 555 nm	Cyanhemoglobin 540 nm	Cyanhemoglobin 546 nm	Cyanide-free photometric measurement
HCT	(RBC x MCV)/10	Total RBC pulse height	(RBC x MCV)/10	(RBC x MCV)/10	(RBC x MCV)/10
MCV	Derived from RBC Histogram	(Hct/RBC) x 10	Derived from RBC Histogram	(Hct/RBC) x 10	(Hct/RBC) x 10
MCHC	(HGB/HCT) x 100	(HGB/HCT) x 100	(HGB/HCT) x 100	(HGB/HCT) x 100	(HGB/HCT) x 100
RET	Supravital staining light scatter	Fluorescent dye light scatter	Supravital staining light scatter	Fluorescent dye light scatter	Fluorescent dye light scatter
PLT	Light scatter and impedance	Light scatter and impedance	Light scatter and impedance	Light scatter	Impedance

WBC: white blood cell, RBC: red blood cell. HGB: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, RET: Reticulocyte, PLT: platelet.

significantly higher in patients than in controls.[19] Hon et al. reported that erythrocyte membrane fluidity was impaired in MS.[20] In another study, they reported an inverse correlation between RBC count and disease duration or disability status scale in MS patients. They also found that MS patients had significantly lower hemoglobin concentrations compared to healthy people.[21]

A study of 187 MS patients and 200 controls revealed significant differences in the prevalence of anemia between patients and controls. Furthermore, MS risk was seven times higher in anemic men and two times higher in anemic women.[22] Fingolimod is a highly effective immunomodulatory drug and the first oral treatment for relapsing-remitting MS. Among other mechanisms, it shows diverse therapeutic effects on cell survival, from inducing apoptosis to protecting against cell death. The use of fingolimod in MS patients has been demonstrated to reduce Hct, Hb, and RBC levels as well as lymphocytes and platelets.[23,24]

White Blood Cell

With the development of flow cytometer and radio waves method in complete blood count devices, the "5-part leukocyte differential" (neutrophils, eosinophils, basophils, monocytes and lymphocytes) could be determined. Neutrophils, one of the leukocyte groups, form the body's first line of defense against bacterial and viral infections and phagocytize microorganisms, dead tissues and debris. A decrease in neutrophils number, which constitute the majority of leukocytes, increases the risk of infection.[25] Eosinophils are especially involved in defense against parasitic infections and their numbers increase in allergic conditions together with basophils.[16] Monocytes are the circulating precursors of macrophages in tissues and the first cell to come into contact with the pathogen.[26] Lymphocytes are produced in the bone marrow like neutrophils and can fulfill their functions after the maturation process. B lymphocytes complete the maturation process in the lymphoid tissue associated with the digestive system and T lymphocytes in the thymus. They then pass into the bloodstream and some of them function in secondary lymphoid organs such as lymph nodes and spleen.[27,28]

Various studies have been conducted on the role of leukocytes and their subgroups in MS pathogenesis and their use as biomarkers. In a study of 127 MS patients divided into two groups (Expanded disability status scale, EDSS <5 (n=90) and EDSS ≥5 (n=37)) and a significant increase in neutrophil/lymphocyte (NLR) ratio was found in patients with EDSS ≥5. A high NLR ratio in MS was thought to increase inflammation and cause an elevated EDSS score.[29] Increased neutrophil activation is thought to be a result of the chronic inflammatory environment, according to Naegele et al.[30,31] Pierson et al. showed that neutrophils play a role in MS pathogenesis and that neutrophils number and activity are increased in Relapsing-Remitting MS patients in contrast to healthy controls. It is claimed that neutrophils contribute to MS pathogenesis by increasing cytokine production and causing damage to the blood-brain barrier.[32,33]

Akaishi et al. reported that leukocyte, monocyte, basophil, and neutrophil counts were higher in MS patients compared to healthy controls before treatment and during attacks. However, no difference was found in terms of lymphocyte levels. These results suggested that the immune system may be systemically altered from the early stages of MS and that innate immunity may play a role in some steps of disease development and progression.[34]

In another study on neutrophils and monocytes, which represent the first line of the innate immune system, leukocytes were phenotyped by flow cytometry, and it was found that granulocytes, $CD15^+$ neutrophils, and monocytes were enlarged while lymphocytes were decreased in relapsing-remitting MS patients. It was thought that the phenotype differences might help earlier diagnosis of these patient.[35]

Platelets

Platelets are one of the parameters investigated for MS and play a primary role in the pathophysiology of central nervous system diseases. Platelets, evaluated in hemogram tests, can activate leukocytes indirectly through biologically active compounds secreted from their granules or directly by binding to the receptor. They are the most numerous cells in the circulatory system after erythrocytes. It is thought that many cytokines and chemokines in their structure play an important role in hemostasis, inflammation, and leukocyte activation.[36] Recent studies have revealed that platelets contribute to the immune system and interact with other immune cells (neutrophils, macrophages, etc.). Since platelets in inflamed neural tissues can adhere to these immune cells, they may cause increased inflammation by recruiting leukocytes.[37-39] Starossom et al. suggested that platelets promote neuro-inflammation and contact with immune cells in MS.[40]

Platelets are the main effector cells in hemostasis, coagulation, and pathological thrombosis. As a result, their role in coagulation and inflammation may be associated with increased vascular risks in MS patients.[41] Additionally, changes in platelet RNA expression profiles were also detected in MS patients.[42] MS is a disease that affects only humans. However, researchers have identified several animal models that can cause MS. The most commonly used models are encephalomyelitis and the cuprizone model.[41] Langer et al. induced chronically activated demyelinating lesions in experimental encephalomyelitis animal models. Histological examinations of the brain and spinal cord showed that platelets accumulated in these lesions and platelet counts increased in the blood.[43]

In a different study involving 253 individuals (126 MS and 127 controls), leukocyte, lymphocyte, and neutrophil values were significantly lower in the MS group. In contrast, platelet volume (MPV), platelet distribution width (PDW), and platelets (PLT) were significantly higher.[44]

Conclusion

Early diagnosis and prediction of prognosis are vital for multiple sclerosis patients. Although studies have identified many biomarkers that could be used for these purposes, none have yet entered routine use. In this review, we examined some studies evaluating the relationship between complete blood count and MS. Accordingly, we found that some hematologic parameters showed variability in patients compared to healthy controls and may be associated with prognosis. However, despite all these studies, we believe that additional studies are needed on the changes in complete blood count parameters in MS. These factors will be more helpful in identifying and treating the condition in future studies.

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CMJ.2024;46(1): 13-18
DOI: 10.7197/cmj.1441696

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

What is Intuitive Eating?: A Review

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Review

History

Received: 24/02/2024
Accepted: 27/03/2024

ABSTRACT

Eating-related behaviors are affected by many factors such as genetics, environment, emotional state, sociodemographic characteristics, religious and cultural beliefs, media, and body perception. As stated, eating behavior, which is affected by many factors, appears to be closely related to emotional factors such as excitement, boredom, happiness and stress. Nowadays, the importance of developing intuitive eating skills in ensuring the formation of healthy eating behaviors instead of unhealthy eating behaviors is emphasized and the use of intuitive eating as an intervention technique is considered important. It is thought that intuitive eating can be an alternative to calorie-restricted diets in the prevention, treatment and body weight management of eating disorders and can also be used together with traditional methods. In this review, literature information about the concept of intuitive eating and its effect on body weight and eating disorders will be presented.

Keywords: Eating behavior, Intuitive eating, Obesity, Eating disorders

Sezgisel Yeme Nedir?: Bir Gözden Geçirme

Derleme

Süreç

Geliş: 24/02/2024
Kabul: 27/03/2024

ÖZET

Yeme ile ilgili davranışlar genetik, çevre, duygusal durum, sosyodemografik özellikler, dini ve kültürel inançlar, medya, beden algısı gibi pek çok faktörden etkilenmektedir. Belirtildiği gibi birçok faktörden etkilenen yeme davranışının heyecan, can sıkıntısı, mutluluk, stres gibi duygusal faktörlerle yakından ilişkili olduğu görülmektedir. Günümüzde sağlıksız yeme davranışlarının yerine sağlıklı yeme davranışlarının oluşmasını sağlamada sezgisel yeme becerisinin gelişmesinin önemi üzerinde durulmakta ve sezgisel yemenin müdahale tekniği olarak kullanılması önemsenmektedir. Sezgisel yemenin, yeme bozukluklarının önlenmesinde, tedavisinde ve vücut ağırlığı yönetiminde kalori kısıtlı diyetlerin alternatifi olabileceği, ayrıca geleneksel yöntemlerle birlikte kullanılabileceği düşünülmektedir. Bu derlemede, sezgisel yeme kavramı ve bu kavramın vücut ağırlığı ve yeme bozuklukları üzerindeki etkisi hakkında literatür bilgileri sunulacaktır.

Anahtar Kelimeler: Yeme davranışı, Sezgisel yeme, Obezite, Yeme bozuklukları

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How to Cite: Bostan Bendaş D, Hocaoğlu Ç. What is Intuitive Eating?: A Review. Cumhuriyet Medical Journal. 2024;46(1):13-18.

Introduction

Eating behaviors and habits begin to develop at an early age. During this process, the relationship between eating behavior and emotions has become a subject of interest for those working in this field. Eating behavior, essential for life, can lead to problems such as eating less or more than necessary or eating disorders.[1] Inadequate coping mechanisms for daily stress can lead to unhealthy eating habits. It is understood from this that an individual's psychological traits can influence their eating behaviors. The influence of psychological traits on eating behavior is not only observed in obese or overweight individuals but also in those perceived to have an ideal body weight. Unhealthy eating habits can also emerge in those who follow prolonged and inappropriate diets.[1-3] In recent years, there has been discussion about certain eating behaviors to be aware of and manage changes in food consumption related to individuals' emotions.[4] It is emphasized that developing intuitive eating skills is important for changing eating attitudes and behaviors towards health, especially in weight control and the treatment of eating disorders.[5] This review will present literature information on the concept of intuitive eating and its impact on body weight and eating disorders.

Definition and History

Intuitive eating is defined as a style of eating that is not driven by emotional desires but by listening to and adapting to the physical signals of hunger and satiety, which are natural responses of the body.[6,7] Intuitive eating emerges as an eating attitude where the individual can stop eating after consuming enough food to satisfy physiological hunger.[8,9] The concept of intuitive eating was defined by Tribole and Resch in 1995.[10] Starting to eat intuitively is a challenging process that requires replacing old dietary habits with new ones.[11] Innate body awareness is hindered by diets, being forced to finish one's plate in childhood, eating because 'it is dinner time', restaurants serving overly large portions, and advertisements that prompt eating irrespective of hunger. The main principles of intuitive eating are to reacquire 'body wisdom'; when this occurs, a person typically eats when hungry and stops when full. Except for certain health conditions (e.g., diabetes, food allergies), there are no restrictions on the types of food you can eat.[6,8,9,12,13] The concept of intuitive eating is based on three fundamental approaches: 1. Unconditional permission to eat, 2. Eating based on physical rather than emotional reasons, 3. Eating in response to physical hunger and satiety signals.[14,15] According to Tribole and Resch, intuitive eating can be explained with 10 principles. These 10 principles include rejecting the diet mentality, challenging the food police, making peace with food, honoring one's hunger, feeling satiety, dealing with emotions without using food, discovering the satisfaction factor, respecting your body, feeling the difference with exercise, and honoring your health with gentle nutrition. These principles aim to abandon old eating attitudes, dismantle dietary taboos, and rediscover the innate skills of intuitive eating.[10,16] Studies have shown that intuitive eating improves cholesterol levels, blood pressure, and insulin sensitivity.[17-19]

Diagnostic Evaluation

The behavior of intuitive eating is identified using the Intuitive Eating Scale developed to assess adaptive eating attitudes as an alternative to maladaptive eating behaviors.[6] The first Intuitive Eating Scale was developed by Hawks et al. in 2004.[16] It was revisited by Tylka in 2006,[6] and in 2013, Tylka and Kroon Van Diest revised the scale to develop the Intuitive Eating Scale-2 (IES-2).[10] This scale comprises twenty-three items and four subscales: (i) eating in response to physical rather than emotional triggers, (ii) unconditional permission to eat, (iii) reliance on hunger and satiety cues, and (iv) body-food choice congruence. The scale is scored according to a 5-point Likert scale (1=strongly disagree, 5=strongly agree). Higher scores indicate a higher propensity for intuitive eating.[15] The Turkish adaptation of the scale, along with its validity and reliability, was conducted by Bas et al. in 2017.[20]

The Relationship Between Intuitive Eating and Obesity

Obesity, whose prevalence is increasing worldwide, is associated with various factors such as age, gender, physical activity, food intake, and eating behavior.[21] Especially today, individuals' eating behaviors play a significant role in the development and prevention of obesity and related diseases.[21,22] The tendency to consume high-calorie and high-fat foods, significant in the development of obesity, increases among individuals with emotional problems.[23] Known treatments for obesity typically focus on interventions that restrict calories and increase physical activity.[24] Recently, certain eating behaviors have been emphasized to be aware of and manage changes in food consumption related to individuals' emotions. Intuitive eating is one of the eating behaviors highlighted in the prevention of obesity.[4] Due to its focus on physical hunger and providing cues on the quantity of food to be consumed, intuitive eating behavior is reported to be negatively associated with body weight and body mass index (BMI), suggesting it could contribute to obesity prevention and treatment.[25,26] In the 1990s, intuitive eating became a new treatment paradigm for obesity in the United States.[8] Evidence suggests that mindfulness-based eating intervention can lead to significant changes in weight, eating behavior, and psychological distress in obese individuals.[12] While traditional dieting may initially lead to weight loss followed by weight gain, evidence also suggests that intuitive eating interventions can support weight maintenance.[27-32] Moreover, completing an intuitive eating program can also result in weight loss.[33] When

exploring the effect of intuitive eating on environmental factors like portion size, it was found that individuals with higher levels of intuitive eating consumed less food, and portion sizes decreased.[34] In various studies investigating the relationship between intuitive eating and BMI, it was found that individuals with a normal BMI had higher intuitive eating scores compared to those who were overweight or obese.[35-37] Among young adults, an inverse relationship between BMI and intuitive eating has been demonstrated.[38,39] Another study found a strong association between eating in response to hunger and satiety cues and lower BMI in middle-aged women, partially influencing the frequency of binge eating.[40] Other studies also demonstrate the association between intuitive eating and a reduction in body weight.[9,41-44] In a study aimed at evaluating the relationship between intuitive eating behaviors among adults in relation to obesity-associated disease risk and gender through anthropometric measurements, a negative correlation was found between IES-2 scores and body weight, BMI, waist-to-height ratio, and waist-to-hip ratio.[45] Intuitive eating is negatively correlated with BMI in cross-sectional studies.[10,33,41-47] Individuals with a high propensity for intuitive eating showed lower BMI, higher high-density lipoprotein (HDL) cholesterol, lower triglycerides, and lower cardiovascular risk compared to individuals with a low propensity for intuitive eating.[46] A study investigating how postmenopausal women classified as overweight or obese experienced the intuitive eating process and the barriers and facilitators they encountered in their daily lives showed that, despite being challenging to implement, the intuitive eating approach was generally well received by participants.[53] In the NutriNet-Santé cohort, involving a total of 11,774 men and 40,389 women aged ≥18, levels of intuitive eating were collected using the validated French version of IES-2. Higher intuitive eating scores were strongly associated with lower rates of overweight and obesity in both men and women.[26] In contrast, a 6-week study evaluating the anthropometric measurements of obese adults using calorie restriction and intuitive eating to achieve weight loss found that the calorie restriction approach was superior to intuitive eating for achieving weight loss, with the calorie restriction group losing significantly more weight. Additionally, some participants in the intuitive eating group began to regain weight during the study.[54]

The Relationship Between Intuitive Eating and Eating Disorders

Using diets as a tool for weight loss is common among college students. It has been found that female undergraduate students engage in disordered eating behaviors such as unhealthy weight control methods throughout college. A study conducted on 638 college students found that 22% ate according to weight loss diets, 3% fasted or took diet pills, 2% chewed and spit out their food or took laxatives, and 1% used diuretics.[55] Another study found that a significant portion of the college population engaged in excessive exercise and binge eating, with the desire to lose weight being the strongest predictor of disordered eating.[56] Cognitions related to restricting calorie intake with the intent to manipulate body weight can increase the risk of developing negative psychological effects such as eating disorders, obsessive concern about weight and body shape in high-risk individuals.[57-61] There is limited research on intuitive eating among individuals with eating disorders. Intuitive eating is negatively associated with disordered eating behaviors in healthy adolescents and adults.[62] Intuitive eating is associated with a more positive body image, more positive emotions, and consequently, a lower risk of eating disorders.[63] It also shows a negative correlation with the adoption of thinness ideals and body dissatisfaction.[6] Individuals with intuitive eating skills tend to exhibit behaviors leading to weight gain to a lesser extent compared to individuals with lower intuitive eating skills.[8] Intuitive eating is considered a valuable intervention target for improving psychological health and reducing disordered eating behaviors, especially binge eating.[64] It has been found that women with eating disorders such as anorexia nervosa, bulimia nervosa, and binge eating disorder have significantly lower scores on the full scale of intuitive eating compared to those without an eating disorder diagnosis.[65] A study exploring the role of intuitive eating in the treatment and recovery of eating disorders found that women who showed full recovery had significantly higher intuitive eating scores compared to those with partial recovery or ongoing eating disorders, and their scores were not different from healthy controls.[66] While intuitive eating is associated with greater weight stability, rigid and flexible control are linked to greater weight variability.[67] Body appreciation has been identified as a protective factor in the development of eating disorders.[68] and is a component of positive body image focusing on respecting, accepting, endorsing, and thinking positively about one's body.[69] Interventions based on physical acceptance and intuition have been shown to effectively reduce the risk of developing eating disorders, excessive weight loss, dietary restrictions, and the internalization of thoughts about psychological disorders.[70] Intuitive eating is a component of body acceptance interventions designed for women with high body weight and symptoms of eating disorders; these women stabilized their weight and reduced symptoms of eating disorders, and improved body image and metabolic condition after the intervention and at follow-up.[27,71] A study investigating the impact of a five-week intuitive eating intervention on dietary restraint, body appreciation, and intuitive eating among female undergraduate students provided preliminary data suggesting that intuitive eating intervention could help mitigate disordered eating risk factors by reducing dietary restraint and increasing intuitive eating.[72] A survey revealed that most Chinese female university students perceived low weight as ideal and were inclined to adopt strict dieting rules, thereby increasing the risks of body dissatisfaction and eating disorders.[73] In a study where 66

women in China participated in an 8-week online and face-to-face intuitive eating intervention consisting of eight modules, evaluating their eating behaviors, symptoms of eating disorders, intuitive eating, and eating flexibility, significant effects of the intervention were found on both groups, promoting positive body image and intuitive eating, and reducing negative body image and disordered eating behaviors.[74] A 10-week intuitive eating and mindfulness training intervention conducted with 93 university students and staff in the United States increased participants' body appreciation and decreased the likelihood of problematic eating behaviors.[75] In a study conducted in a residential treatment center for women receiving treatment for eating disorders, the effects of an intuitive eating intervention were explored, and it was found that intuitive eating scores significantly increased for all diagnosed eating disorders studied. At discharge, higher intuitive eating scores were associated with better clinical outcomes, including fewer symptoms of eating disorders, less body image concerns, and psychological symptoms.[76] A 10-week intervention study following the 10 core principles of intuitive eating, involving 61 participants, observed that participants moved away from the concept of 'dieting' by the end of the program, indicating that intuitive eating interventions could be beneficial in treating individuals with binge eating disorder.[31] Programs supporting intuitive eating have been stated to reduce the frequency of overeating or binge eating and contribute to the development of healthy eating behaviors.[14] In a systematic review of 20 different studies on interventions promoting intuitive eating, it was found that intuitive eating interventions reduced binge eating and led to better responses to hunger and satiety cues.[44] Another study observed a strong protective effect of intuitive eating against binge eating. An initial higher score in intuitive eating was associated with a 74% lower likelihood of binge eating at follow-up, and an increase of one point in intuitive eating scores during follow-ups was associated with a 71% lower likelihood of binge eating.[64] A study examining the extent to which obese individuals differ from those of normal weight and overweight in emotional and addiction-like eating behaviors reported that the two groups with higher BMI indicated higher levels of depressive mood, ate more in response to negative emotions but less intuitively, and exhibited more severe and/or frequent symptoms of addiction-like eating behaviors compared to normal-weight individuals.[77] A study with 200 women aged 60-75 aiming to explore the relationships between body image, intuitive eating, and eating showed that higher scores of intuitive eating were associated with lower restriction, lower eating concern, lower body concern, fewer depressive symptoms, and lower BMI. An indirect relationship emerged between BMI and intuitive eating through concerns about weight and shape, suggesting that preoccupation with appearance might impede the practice of intuitive eating. These findings suggest that intuitive eating is associated with positive outcomes among older women and could be a valuable target for interventions designed to promote healthy aging.[78] Overall, intuitive eating is inversely related to symptoms of eating disorders.[79,80]

Conclusion

Intuitive eating appears to be significant both in the management of body weight and in the treatment and prevention of eating disorders. Interventions based on intuitive eating can be used alongside other methods for weight management and the prevention and treatment of eating disorders. Such emerging therapeutic approaches are thought to hold promise, especially for the positive change in eating behaviors, including weight management and the treatment of eating disorders. Further comprehensive studies in this field are needed.

Conflict of Interest

The authors declare no conflict of interest.

Financial Support

None.

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CMJ.2024;46(1):19-22
DOI: 10.7197/cmj.1431097

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Our Experience with Emergency Surgery in Geriatric Patients

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Research Article

History

Received: 03/02/2024
Accepted: 02/03/2024

ABSTRACT

Objective: A significant portion of admissions to emergency departments are made up of elderly patients. We aim to determine the causes of acute abdomen in geriatric patients requiring emergency surgery, evaluate postoperative intensive care needs and mortality rates, and raise awareness about this patient group.

Methods: Patient files of individuals aged 65 and older who were consulted in our hospital's emergency department and subsequently admitted to the general surgery service between 2021 and 2023 were retrospectively reviewed. Data including age, gender, underlying diseases, additional illnesses, duration of stay in the intensive care unit, cause of mortality, and length of hospital stay were extracted from the patient's records. The collected data were analyzed statistically for comparisons.

Results: Data of 27 patients were accessed.these patients, 40.7% (n=11) were female, and 59.3% (n=16) were male. The average age of the patients was determined to be 74.81 years (ranging from 65 to 88). Thirteen patients, comprising 5 males and 8 females, were monitored in the intensive care unit. 6 patients experienced mortality, and all of them were those admitted to the intensive care unit. When comparing mortality rates based on gender, it was 18.8% in male patients and 27.3% in female patients. All 27 patients had at least one comorbidity. Patients who experienced mortality had at least two comorbidities. Twelve patients did not undergo surgery.

Conclisions: In the emergency assessment of geriatric patients, a prompt diagnosis should be made, considering comorbidities after diagnosis, and follow-up and treatments should be adjusted multidisciplinary for patients requiring intensive care or those to be monitored in regular rooms.

Keywords: Geriatric patient, Emergency surgery, Mortality

Geriatrik Hastalarda Acil Cerrahi Tecrübemiz

Araştırma Makalesi

Süreç

Geliş: 03/02/2024
Kabul: 02/03/2024

ÖZET

Amaç: Acil servislere başvuruların önemli bir kısmını yaşlı hastalar oluşturmaktadır. Acil cerrahi gerektiren geriatrik hastalarda akut karın nedenlerini belirlemeyi, postoperatif yoğun bakım ihtiyaçlarını ve mortalite oranlarını değerlendirmeyi ve bu hasta grubu hakkında farkındalık yaratmayı amaçlıyoruz.

Yöntem: 2021-2023 yılları arasında hastanemiz acil servisine başvuran ve sonrasında genel cerrahi servisine yatırılan 65 yaş ve üzeri bireylerin hasta dosyaları geriye dönük olarak incelendi. Hasta kayıtlarından yaş, cinsiyet, altta yatan hastalıklar, ek hastalıklar, yoğun bakımda kalış süresi, ölüm nedeni, hastanede kalış süresi gibi veriler elde edildi. Toplanan veriler karşılaştırmalar için istatistiksel olarak analiz edildi

Bulgular: 27 hastanın verilerine ulaşıldı. Bu hastaların %40,7'si (n=11) kadın, %59,3'ü (n=16) erkekti. Hastaların yaş ortalaması 74,81 (65 ile 88 arasında) olarak belirlendi. Yoğun bakım ünitesinde 5 erkek, 8 kadın olmak üzere 13 hasta izlendi. 6 hastada ölüm yaşandı ve bunların tamamı yoğun bakım ünitesine yatırılan hastalardan oluştu. Cinsiyete göre ölüm oranları karşılaştırıldığında erkek hastalarda bu oran %18,8, kadın hastalarda ise %27,3 oldu. 27 hastanın tamamında en az bir komorbidite mevcuttu. Mortalite yaşayan hastaların en az iki komorbiditesi vardı. On iki hasta ameliyat edilmedi.

Sonuç: Geriatrik hastaların acil değerlendirmesinde, tanı sonrası komorbiditeler göz önünde bulundurularak hızlı tanı konulmalı, yoğun bakım gerektiren veya normal odalarda izlenecek hastalar için takip ve tedaviler multidisipliner olarak ayarlanmalıdır.

Anahtar Kelimeler: Yaşlı hasta, Acil cerrahi, Ölüm

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How to Cite: Soylu S. Our Experience with Emergency Surgery in Geriatric Patients. Cumhuriyet Medical Journal. 2024;46(1):19-22.

Introduction

Geriatrics is characterized by a decline in an individual's adaptability to changing environments and a diminishing capacity to maintain a balance between internal and external factors, increasing the likelihood of mortality, as defined by the World Health Organization (WHO).

It is projected that by the year 2050, the global average life expectancy will rise to 77.1 years.[1] The world's population is rapidly aging, with approximately 9% of Turkey's population currently being 65 years and older.[2] This demographic shift is accompanied by a growing demand for healthcare services for individuals aged 65 and above.

Geriatric patients constitute 23% of all surgical procedures, facing a high risk of morbidity and mortality during both elective and emergency surgeries.[3] The increasing geriatric population has resulted in a rise in emergency department visits by elderly patients. Advances in surgical methods and techniques, along with improvements in postoperative care, have contributed to an increased frequency of surgical interventions in the geriatric population.[4] Aging often comes with associated chronic illnesses, predicting a substantial increase in morbidity, mortality, and the need for intensive care support.

One of the most complex issues in emergency departments is abdominal pain in the geriatric age group.[5] The accuracy of diagnosis in geriatric patients in the emergency department ranges from 40% to 82%.[6,7] The difficulty in diagnosis primarily stems from the fact that typical clinical symptoms may manifest differently in geriatric patients. Leukocytosis and fever may occur later in elderly patients, and the degree of fever is lower compared to younger individuals. Medications used by elderly patients can also yield complex results in vital signs.[8] Clinical presentations are often milder in elderly patients compared to younger ones. Obtaining a thorough medical history may be challenging due to factors such as hearing difficulties and dementia.[9,10] Moreover, typical examination findings may be absent, and a surgical pathology may be overlooked even when laboratory values are within the normal range.[11] Various medications used by elderly patients can also mask acute abdominal symptoms. In addition to the abdominal examination, a systemic examination should be carefully conducted in elderly patients. Furthermore, examinations targeting systemic diseases that could alter abdominal findings should be performed.

In this study, we aim to identify the causes of acute abdomen in geriatric patients requiring emergency surgery, assess their postoperative intensive care needs and mortality rates, and raise awareness about this patient group.

Materials and Methods

Ethical approval for the study was obtained from the non-interventional ethics committee of Cumhuriyet University under approval number 2023-12/43 on December 21, 2023. Following ethical approval, the study commenced. Patient files of individuals aged 65 and older who were consulted in our hospital's emergency department and subsequently admitted to the general surgery service between 2021 and 2023 were retrospectively reviewed.

Data including age, gender, underlying diseases, additional illnesses, duration of stay in the intensive care unit, cause of mortality, and length of hospital stay were extracted from the patient's records. The collected data were analyzed statistically for comparisons. The statistical software tool SPSS 23.0 was used to make statistical comparisons (SPSS Inc., Chicago, IL, USA). The Mann Whitney U test was performed to examine the statistical significance of the difference between the group means after it was found that the variables utilized were not suitable for a normal distribution. To compare categorical variables, the chi-squared test.

Results

Data from a total of 27 patients were obtained for analysis. Of these patients, 40.7% (n=11) were female, and 59.3% (n=16) were male. The average age of the patients was determined to be 74.81 years (ranging from 65 to 88). The average age for male patients was 74, while for female patients, it was 77.45. The difference in average age between genders was not statistically significant ($p>0.05$). Thirteen patients, comprising 5 males and 8 females, were monitored in the intensive care unit. No significant difference was found when comparing patients monitored in the intensive care unit by gender ($p>0.05$).

Among the 27 patients, 6 patients experienced mortality, and all of them were those admitted to the intensive care unit. When comparing mortality rates based on gender, it was 18.8% in male patients and 27.3% in female patients, with no statistically significant difference. The overall mortality rate, irrespective of gender, was found to be 22.2%. The causes of mortality included mesenteric ischemia in 2 patients, pancreatic fistula with associated abscess in 1 patient, intestinal obstruction in 1 patient, and perforation in 2 patients (1 gastric perforation, 1 colon perforation).

All 27 patients had at least one comorbidity [Hypertension (HTN), Diabetes Mellitus (DM), Coronary Artery Disease (CAD)]. Patients who experienced mortality had at least two comorbidities. Twelve patients did not undergo surgery, with reasons including cholecystitis in 3 patients, bowel obstruction in 3 patients, gastrointestinal bleeding in 2 patients, liver laceration due to trauma in 1 patient, diverticulitis in 2 patients, and obstructive jaundice in 1 patient (Table 1).

Table 1. Diagnostic Distribution of Patients

Diagnoses	Number of patients(n=)	Percentage(%)	Exitus
Obstruction	3	11.11	1
Cholecystitis	3	11.11	-
Incancered hernia	3	11.11	-
Mesenteric ischemia	3	11.11	2
Gastrointestinal Bleeding	3	11.11	-
Perforation(small bowel+ colon+ p.ulcus)	4	14.8	2
Gastrointestinal Bleeding	2	7.4	-
Acute appendicitis	2	7.4	-
Obstructive jaundice	1	3.7	-
Pancreatic abscess	1	3.7	1
Trauma	1	3.7	-
Volvulus	1	3.7	-
Total	27	100(%)	6

Discussion

Advancements in healthcare worldwide have led to progress in the diagnosis and treatment of chronic diseases such as diabetes, cardiovascular diseases, and lung diseases in the elderly population. Consequently, there is an increasing need for surgical interventions in the aging population, contributing to the extension of human life.[12]

A study by Reiss et al.[13] demonstrated that gender did not significantly impact mortality, aligning with our findings where the mortality rate was 27.3% in females and 18.8% in males, though not statistically significant.

Emergency surgical procedures in the geriatric patient group exhibit higher mortality and complication rates compared to elective procedures.[14] In our study group, the mortality rate was found to be 22.8%. Common comorbidities in the geriatric patient group, such as diabetes mellitus (DM), hypertension (HTN), coronary artery disease (CAD), and malignancies, contribute to increased morbidity and mortality rates. The majority of our patients had comorbidities, with hypertension (HTN) at 96.3%, coronary artery disease (CAD) at 55.6%, and diabetes mellitus (DM) at 44.4%. Lyon reported mortality rates ranging from 15% to 34% following emergency abdominal surgery,[15] while Juan found a mortality rate of 22%. Postoperative pneumonia, cardiac complications, and sepsis are well-known contributors to mortality in these cases. In our patient group, the mortality rate was determined to be 22.2%. The presence of an underlying chronic condition in patients undergoing emergency surgery negatively affects prognosis, leading to higher mortality compared to elective surgery.

Diseases causing acute abdomen in geriatric patients differ from those in younger individuals. Reduced physiological capacity has negative effects on the symptoms and signs of the medical condition, leading to delayed diagnosis or a more complex perioperative period. Another challenge in geriatric patients is the difficulty in obtaining sufficient medical history due to issues such as memory loss and hearing impairments.[16]

Reviewing the cases, it is noted that the majority involve acute cholecystitis. In this study, the most common causes of acute abdomen were acute cholecystitis and mechanical intestinal obstruction, followed by incarcerated hernias, mesenteric ischemia, and gastrointestinal bleeding, respectively.[16]

Acute cholecystitis is a significant cause of abdominal surgery in the geriatric population, leading to high morbidity and mortality.[17] Surgical treatment is recommended for symptomatic gallstone patients regardless of age. Only one patient in this study underwent emergency surgery, while the other two were electively operated on later. One patient declined elective surgery despite recommendations.

Incarcerated hernia is another common reason for surgery in the geriatric population. Patients with hernias who are not recommended for elective surgery due to accompanying diseases or advanced age may require emergency surgery when presenting with symptoms of incarcerated or strangulated hernias. Desunkami reported a frequency of 14% for gangrenous intestinal necrosis caused by strangulation.[18] In our study, none of the three incarcerated hernia patients required resection, all received intensive care support, and there were no mortalities.

Mechanical intestinal obstruction constitutes 15-20% of all emergency surgical cases in geriatric patients.[19,20] The incidence of colon cancer increases with age, with those aged 65 and above having about five times higher rates than younger individuals.[21] Another major cause of mechanical intestinal obstruction is obstruction resulting from postoperative adhesions, constituting 7.4% of all obstruction cases. Sigmoid volvulus, particularly common in the elderly, is the most frequent type of colon volvulus (75-80%).[15] Three patients in our study had developed mechanical intestinal obstruction due to intra-abdominal bridles, and one due to volvulus. None of the bridled patients required surgery and were successfully managed with medical treatment.

Mesenteric vascular occlusions are common in elderly patients, especially those with cardiovascular diseases. Mesenteric ischemia accounts for 10% of indications for emergency acute abdomen in the elderly.[22] Mamode reported an 81% mortality rate in mesenteric vascular occlusions.[23] In our study, three patients experienced mesenteric ischemia with a high mortality rate of 66.6%.

Although acute appendicitis is more common in younger patients, it can present less frequently in the geriatric population. Atypical presentation of appendicitis symptoms in geriatric patients may result in delayed diagnosis, potentially leading to perforated appendicitis. Two patients in our study underwent surgery due to appendicitis. Both cases were diagnosed without perforation, treated without complications, and had no postoperative issues.

Our study has limitations, the patient population included in the study is relatively small, and further studies are needed.

In conclusion, examining the 27 patients included in this study (n=14), it is observed that 51.85% of patients underwent surgery, almost all patients had comorbidities, and among patients requiring intensive care, 77.7% had at least one accompanying comorbidity. In the emergency assessment of geriatric patients, a prompt diagnosis should be made, considering comorbidities after diagnosis, and follow-up and treatments should be adjusted multidisciplinary for patients requiring intensive care or those to be monitored in regular rooms.

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CMJ. 2024; 46(1):23-28
DOI: 10.7197/cmj.1382874

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Evaluation of Antibody Response After COVID-19 Vaccination in Healthcare Workers: A Turkish Tertiary Hospital Experience

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Research Article

History

Received: 29/10/2023
Accepted: 20/03/2024

ABSTRACT

Objective: It was aimed to explore the correlation between demographic characteristics and the presence of comorbidity in the antibody response after the second dose of vaccination in healthcare workers in this study. In addition, the third and fourth dose approaches of the participants and the protection of the antibody levels formed by the two doses of vaccine against COVID-19 were examined observationally.
Methods: Health workers, whose NCP and S protein antibody levels were detected on the 30th day after the second dose of the CoronaVac vaccine, were followed up in terms of being vaccinated for the third and fourth doses and having COVID-19.
Results: Higher levels of S antibodies were detected in women after two doses of vaccination (*p=0.001*). It was pointed out that smoking has a negative effect on the antibody response after vaccination (*p=0.008*). People who had pre-vaccine COVID-19 had higher NCP antibody levels after two doses of vaccination (*p=0.013*). Of the participants, 152 (97.4%) were vaccinated with the third dose and 110 (70.5%) with the fourth dose.
Conclusion: The antibody response after two doses of inactivated CoronaVac® vaccination probe is significantly higher in women, younger people, non-smokers, and people who have not been previously infected with the SARS-CoV-2.

Keywords: COVID-19 Vaccines, Vaccine, Antibody Response, Protection, Healthcare Workers

Sağlık Çalışanlarında COVID-19 Aşısı Sonrası Antikor Yanıtının Değerlendirilmesi: Türkiye'de Üçüncü Basamak Bir Hastane Deneyimi

Araştırma Makalesi

Süreç

Geliş: 29/10/2023
Kabul: 20/03/2024

ÖZET

Amaç: Bu çalışmada sağlık çalışanlarında ikinci doz aşılama sonrası antikor yanıtında komorbidite varlığı ile demografik özellikler arasındaki ilişkinin araştırılması amaçlanmıştır. Ayrıca katılımcıların üçüncü ve dördüncü doz yaklaşımları ile iki doz aşının COVID-19'a karşı oluşturduğu antikor düzeylerinin koruyuculuğu gözlemsel olarak incelenmiştir.
Yöntem: CoronaVac aşısının ikinci dozundan sonraki 30. günde NCP ve S protein antikor düzeyleri saptanan sağlık çalışanları, üçüncü ve dördüncü doz aşılarını yaptırmaları ve COVID-19'a sahip olmaları açısından takibe alınmıştır.
Bulgular: İki doz aşılamadan sonra kadınlarda daha yüksek S antikorları saptanmıştır (*p=0.001*). Sigaranın aşılama sonrası antikor cevabını olumsuz etkilediğine dikkat çekilmiştir (*p=0,008*). Aşı öncesi COVID-19 enfeksiyonu olan kişilerin, iki doz aşılamadan sonra daha yüksek NCP antikor seviyelerine sahipolduğu belirlendi (*p=0.013*). Katılımcıların 152'si (%97,4) üçüncü doz, 110'u (%70,5) dördüncü doz ile aşılanmıştır.
Sonuç: İki doz inaktif CoronaVac® aşılama probu sonrası antikor yanıtı, kadınlarda, gençlerde, sigara içmeyenlerde ve daha önce SARS-CoV-2 ile enfekte olmamış kişilerde anlamlı olarak daha yüksektir.

Anahtar Kelimeler: COVID-19 Aşıları, Aşı, Antikor Yanıtı, Koruma, Sağlık Çalışanları

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How to Cite: Çubuk F, Aslan R, Hasbek M, Taşkın Kafa AH. Evaluation of Antibody Response After COVID-19 Vaccination in Healthcare Workers: A Turkish Tertiary Hospital Experience, Cumhuriyet Medical Journal. 2024;46(1):23-28.

Introduction

The SARS-CoV-2 virus, which arose in December 2019 in China, quickly affected the whole world, causing the Coronavirus disease 2019 (COVID-19) pandemic. This pandemic has caused millions of deaths around the world, with portentous effects on the national health systems and the global economy. This situation has led to searches to control the devastating effects of the pandemic and to provide social immunity against the COVID-19 disease. Today, many vaccines have been developed against COVID-19 using different health technologies.[1,2]

COVID-19 vaccines have been very beneficial in preventing infectious diseases, reducing mortality, and controlling the pandemic.[3] In addition, the route of the COVID-19 pandemic and how effective the vaccines will show against possible new variants are still a matter of curiosity. [4]

The main goal of COVID-19 vaccine applications is to provide a strong immune response as a result of stimulating the immune system. The immune response that occurs after vaccination includes components such as innate immunity, cellular immunity, humoral immunity, and cytokine response.[5,6] Serological detection of the antibody response resulting from humoral immunity is a convenient method that can be used to determine the presence and level of the immune response after vaccination.[7] In serological tests, using purified SARS-CoV-2 proteins such as the nucleocapsid protein (NCP) and spike (S) protein, or more specific subregions such as the S1 and S2 subunits or the receptor binding domain (RBD) in the S1 subunit, the presence of virus-specific IgM, IgG or IgA antibodies in the blood can be determined.[8]

Many test kits have been developed to detect antibodies against SARS-CoV-2. The most important disadvantage of the antibody tests is the inconsistency between the results of the kits in which antibodies against different viral proteins were investigated.[9] In general, it is stated that a better antibody response occurs thanks to COVID-19 vaccines, especially after the second dose. In addition, it is clarified that the immune response that occurs after vaccination is stronger than the immune response that occurs with a natural infection and that people who have had COVID-19 will also benefit from vaccination.[9] On the other hand, factors such as individual characteristics such as age, gender, presence of comorbidities, genetics and nutrition, vaccine type, presence of adjuvant, and vaccine dose may affect the effectiveness of the immune response and the duration of vaccine-induced immunity.[10,11]

Since healthcare workers have a high risk of encountering COVID-19 infection, these individuals have been given priority in the CoronaVac (Sinovac, China) vaccination program in our country. In this study, it was aimed to investigate the relationship between the antibody response after the second dose of vaccination, and gender, age, body mass index, smoking, the presence of COVID-19 history before vaccination, presence of diabetes mellitus, and hypertension in healthcare workers. In addition, it is planned to observationally examine the third and fourth-dose vaccination approaches of the participants and the protection of the antibody levels detected after two doses of vaccination against COVID-19.

Material and Methods

One hundred and fifty-six healthcare professionals were included in this prospective study between the study period, January- December 2021. Two doses of the CoronaVac vaccine were administered to healthcare workers in January and February 2021. The third and/or fourth dose vaccination and COVID-19 status of healthcare workers whose NCP and S protein antibody levels were detected on the 30th day after the second dose of vaccination were followed up to two years until 2023.

3-5 mL of the blood sample taken from volunteer health workers participating in the research were separated into serum by centrifugation. The presence of NCP and S protein antibodies in serum samples were analyzed with Elecsys Anti-SARS-CoV-2 (Roche Diagnostics, Switzerland) and Elecsys Anti-SARS-CoV-2 S kit (Roche Diagnostics, Switzerland) test kits, respectively using the Electro-chemiluminescence Immune Assay (ECLIA) method in the Cobas e601 (Roche Diagnostics, Switzerland) device following the manufacturer's recommendations.

The presence of NCP antibody in serum samples was qualitatively evaluated using the Elecsys Anti-SARS-CoV-2 kit (Roche Diagnostics, Switzerland). IgM and IgG-type antibodies developed against NCP were measured according to the Cut-Off Index (COI) value in accordance with the manufacturer's recommendations. COI < 1; is rated "*nonreactive*", and COI ≥1; is rated as "*reactive*". All antibodies including IgG, against the RBD region of the S protein, were evaluated quantitatively using the Elecsys Anti-SARS-CoV-2 S kit (Roche Diagnostics, Switzerland). In this assessment, results determined as greater than 0.8 U/mL were considered "*reactive*", and the highest antibody value was measured as 250 U/mL by the device. The values measured above 250 U/mL were accepted as >250 U/mL.

Statistical analysis was performed using SPSS 22.0 (IBM Co., USA). In the assessment of the results, antibody levels were grouped as 1-125, 126-250, and >250 U/mL and evaluated as the percent. The difference between the groups was evaluated with the $\chi 2$, Fisher's exact, Mann-Whitney U, and Kruskal-Wallis tests in accordance with the convenience. The value of $p < 0.05$ was considered statistically significant.

Ethical Approval

The study protocol was approved by the Sivas Cumhuriyet University Clinical Research Ethics Committee (Date: 21.12.2020, Decision number: 2020-12/03). Each stage of the research was performed per the ethical standards specified in the 1964 Declaration of Helsinki and its later amendments.

Results

A total of 156 health workers, 77 (49.4%) women, and 79 (50.6%) men, were included in this study. The ages of the participants are between 21-59 years. The mean age of the participants was 36.76±8.9. The mean age of female participants was 36.55±8.3, and of male participants was 36.96±9.5. Among all the participants sixty (38.5%) of them had experienced COVID-19 infection before they were given two doses of the CoronaVac vaccine and 96 (61.5%) had no history of the previous COVID-19 infection. Thirty-three (55%) of the healthcare workers who had COVID-19 infection were female, and 27 (45%) were male. Among participants who had COVID-19 infection before two doses of CoronaVac vaccination, measurable NCP-antibody levels were detected (>1) in 52 cases (86.7%), while measurable NCP antibody levels were not detected in eight cases (13.3%). On day 30, after two doses of CoronaVac vaccination, a total of 155 (99.4%) participants had measurable levels of S antibody (>0.8), and a total of 135 participants (86.5%) had measurable levels of NCP antibodies (>1).

In this study, S antibody was found to be negative after two doses of the CoronaVac vaccine only in one healthcare worker. This person was a 41-year-old female health worker with a body mass index of 29.2. She does not smoke or has no comorbidities. She was not infected with COVID-19 before the CoronaVac vaccination. In this healthcare worker COVID-19 PCR test positivity was detected after the fourth dose of vaccination, whose third and fourth doses were vaccinated with the Pfizer-BioNTech vaccine (BNT162b2).

Table 1 shows the distribution of S antibody levels on the 30th day after two doses of CoronaVac vaccination of healthcare workers included in this study, according to demographic characteristics such as gender, age groups, body mass index, smoking, and comorbidity (Table 1).

Table 1. Distribution of S antibody levels according to demographic characteristics at day 30 after vaccination of the healthcare worker with two doses of CoronaVac.

		S antibody level (n=155)			
		1–125 U/mL	126–250 U/mL	>250 U/mL	
	n		n (%)		*p*
COVID-19 infection status before vaccination					
Yes	60	8 (13.3)	8 (13.3)	44 (73.4)	0.000
No	95	38 (40)	20 (21.1)	37 (38.9)	
Gender					
Woman	76	13 (17.1)	13 (17.1)	50 (65.8)	0.001
Man	79	33 (41.8)	15 (19)	31 (39.2)	
Age groups					
20-29	50	9 (18.0)	7 (14.0)	34 (68.0)	
30-39	43	12 (27.9)	8 (18.6)	23 (53.5)	0.123
40-49	42	17 (40.5)	9 (21.4)	16 (38.1)	
50-59	20	8 (40.0)	4 (20.0)	8 (40.0)	
Body mass index					
Normal (18.5-24.9)	92	30 (32.6)	14 (15.2)	48 (52.2)	
Overweight (25-29.9)	52	13 (25.0)	12 (23.1)	27 (51.9)	0.773
Obesity (≥30)	11	3 (27.3)	2 (18.2)	6 (54.5)	
Smoking					
Yes	83	32 (38.5)	17 (20.5)	34 (41.0)	0.008
No	72	14 (19.4)	11 (15.3)	47 (65.3)	
Diabetes mellitus					
Yes	16	5 (31.3)	3(18.7)	8 (50.0)	0.982
No	139	41 (29.5)	25 (18)	73 (52.5)	
Hypertension					
Yes	18	9 (50.0)	4 (22.2)	5 (27.8)	0.068
No	137	37 (27.0)	24 (17.5)	76 (55.5)	
NCP antibody level					
Nonreactive	20	16 (80.0)	3 (15.0)	1 (5.0)	0.000
Reactive	135	30 (22.2)	25 (18.5)	80 (59.3)	
Total	155	46 (29.7)	28 (18)	81 (52.3)	

Table 2. Vaccination status of healthcare workers

Vaccine	First dose	Second dose	Third dose	Fourth dose
			n (%)	
CoronaVac	156 (100.0)	156 (100.0)	2 (1.3)	0 (0.0)
Pfizer-BioNTech	0 (0.0)	0 (0.0)	150 (96.1)	110 (70.5)
Unvaccinated person	0 (0.0)	0 (0.0)	4 (2.6)	46 (29.5)

S and NCP antibody levels in blood samples taken 30 days after the second dose of vaccination were compared in this study. NCP antibody was found nonreactive; in 16 (34.8%) of the 46 healthcare workers with S antibody levels between 1–125 U/mL; in 3 (10.7%) of 28 healthcare workers with S antibody levels between 126–250 U/mL, and one (1.2%) of 81 healthcare workers with S antibody levels >250 U/mL.

The first, second, third, and fourth dose vaccination statues of the healthcare workers included in this study are given in Table 2. 152 (97.4%) of the participants had the third dose and 110 (70.5%) of the participants had the fourth dose of the vaccine. 46 healthcare workers (29.5%) did not vaccinate with the fourth dose (Table 2).

The distribution of antibody levels and demographic characteristics of healthcare workers with COVID-19 infection after two doses of CoronaVac vaccination according to their history of COVID-19 infection before vaccination is presented in Table 3.

A total of 48 (30.8%) healthcare workers included in the study had COVID-19 infection after two doses of vaccination. In 14 (29.2) of these people, COVID-19 infection history was detected before two doses of vaccination, and COVID-19 infection was diagnosed by PCR test. It was determined that 34 (70.8) healthcare workers did not have COVID-19 infection before vaccination (Table 3).

In this study, it was specifically found that people who had COVID-19 infection before vaccination had higher NCP antibodies after two doses of vaccination (*p=0.013*). On the other hand, there was no difference in S antibody levels after two doses of vaccination between groups with and without COVID-19 infection (*p=0.183*) (Table 3).

Table 3. Distribution of antibody levels and demographic characteristics of healthcare workers who had COVID-19 infection after two doses of vaccination, according to their history of having COVID-19 infection before vaccination.

		Infected COVID-19	Not Infected COVID-19	*p*
	n	n (%)		
COVID-19 period				
After the second dose	9	4 (28.6)	5 (14.7)	
After the third dose	21	5 (35.7)	16 (47.1)	0.515
After the fourth dose	18	5 (35.7)	13 (38.2)	
***Spike antibody**				
<1 U/mL	1	0 (0)	1 (2.9)	
1–125 U/mL	13	2 (14.3)	11 (32.4)	0.183
125-250 U/mL	8	1 (7.1)	7 (20.6)	
>250 U/mL	26	11 (78.6)	15 (44.1)	
***Nucleocapsid antibody**				
<1 U/mL	10	1 (7.1)	9 (26.5)	
1–125 U/mL	30	7 (50)	23 (67.6)	0.013
125-250 U/mL	7	5 (35.7)	2 (5.9)	
>250 U/mL	1	1 (7.1)	0 (0)	
Gender				
Woman	25	6 (42.9)	19 (55.9)	0.412
Man	23	8 (57.1)	15 (44.1)	
Age groups				
20-29	15	5 (35.7)	10 (29.4)	
30-39	14	5 (35.7)	9 (26.5)	0.407
40-49	13	4 (28.6)	9 (26.5)	
50-59	6	0 (0)	6 (17.6)	
Total	48	14 (29.2)	34 (70.8)	

Discussion

Investigating the antibody response to SARS-CoV-2 can provide important data to understand whether people have been infected with this virus before, to diagnose a possible infection, and to determine the impact of the vaccine in case of vaccination.[9] In this study, the relationship between the antibody response after the second dose of vaccination in healthcare workers and history of COVID-19 before vaccination, gender, age, body mass index, smoking, and presence of chronic disease was investigated.

In the literature, it is reported that the immune response that occurs after vaccination is higher than the immune response that occurs with natural infection and that people who have had COVID-19 infection will also benefit from the vaccine.[9] In our study, it was found that the people who had COVID-19 infection before two doses of vaccination had higher antibody levels compared to people without a history of COVID-19 (*p=0.000*). This result is compatible with the literature.

A study conducted by Uysal et al.[12] showed that among 314 healthcare workers S antibody levels were above >250 U/mL in 56% of women and 44% of men after two doses of CoronaVac vaccination. However, they reported

that no significant difference was found between the genders (*p=0.111*). In another study, no difference was found between genders in terms of antibody levels after vaccination.[13] However, in our study, higher S antibody levels were detected in women compared to men after two doses of vaccination (*p=0.001*). Consistent with our study, in a study conducted by Akaret al.[11] in Türkiye, it was reported that the antibody response was found to be significantly higher in women after vaccination. This difference between the gender is considered as usual since the difference in the duration of infection in women and men may affect the humoral immune response after vaccination.[14]

Germinal centers in lymph nodes are highly functional structures for antibody response formation after vaccination. As a result of the decrease in the size and functions of the germinal center with aging, it causes weakening of the humoral response and a decrease in antibody levels after vaccination.[15] In the study of Uysal et al,[12] it was reported that higher antibody levels were detected in the 30-39 age group (38.5%) compared to other age groups. In another study by Seyahi et al,[16] lower antibody levels were observed after two doses of vaccination in people over the age of 65 compared to hospital workers of younger ages. In our study, no statistically significant relationship was found between age groups and antibody levels (*p=0.123*). However, the detection of higher antibody levels in the ages of 20-29 and 30-39 compared to other age groups in our study is similar with the literature.

It has been reported that smoking and high body mass index negatively affect the humoral response to COVID-19 vaccines and cause low antibody response.[11,17,18] In our study, in concordance with the literature, it was determined that smoking had a negative effect on the antibody response after vaccination (*p=0.008*). After two doses of vaccination, antibody levels were >250 U/mL in 65.3% (47/72) of non-smokers and 41% (34/83) of smokers.

Soegiarto et al.[19] pointed out to the associated hypertension with low antibody levels after CoronaVac vaccination. Consistent with this study, lower S antibody levels were found in healthcare workers with a history of hypertension in our study (*p=0.068*). While >250 U/mL of S antibody levels were observed in 27.8% of patients with a history of hypertension, S antibody levels >250 U/mL were detected in more than half (55.5%) of those who did not have this history.

The limitation of our study was that the Elecsys Anti-SARS-CoV-2 S-kit could not be obtained before two doses of CoronaVac vaccination of healthcare workers, so the levels of S antibody before vaccination could not be determined. In addition, only the humoral antibody response of the vaccine was revealed in our study; thus, no information could be given about cellular immunity. In addition, the participants preferred different vaccines for the third and fourth doses. In our study, we could not investigate how and to what extent different vaccine preferences affect the effectiveness of antibody response therefore this could be considered a limiting situation as well.

Conclusion

As a result, the CoronaVac®, which is an inactivated SARS-CoV-2 vaccine, provides an adequate S antibody response as 99.4%, 30 days after two doses of vaccination in healthcare workers aged 21-59 years. The antibody response is significantly higher in women, younger people, non-smokers, and people who have not been previously infected with the SARS-CoV-2 virus. The exact protective effect of the antibody levels obtained with the vaccine are in practice will be better understood in the periods when the number of new cases increases.

Declaration of Conflict of Interest

The authors declared no potential conflicts of interest concerning this article's research, authorship, and publication.

Funding

The authors received no financial support for this article's research, authorship, and publication.

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CMJ. 2024;46(1):29-34
DOI: 10.7197/cmj.1413260

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Effects of Metformin on TNF-α Release in Lipopolysaccharide-Induced Monocytes in Rats

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Research Article

History

Received: 02/01/2024
Accepted: 22/01/2024

ABSTRACT

Objective: Inflammation which is a response of immune system was demonstrated in many disorders such as atherosclerosis, hypertension, diabetes, cancer and rheumatoid arthritis. Metformin, an oral antidiabetic drug, has anti-inflammatory effect apart from blood glucose regulatory effect. However, the mechanism of its anti-inflammatory effect is not clearly understood. In this study, the effect of metformin on the release of cytokines (TNF-α and IL-6) from LPS stimulated rat mononuclear blood cells was investigated.

Methods: Blood samples (5ml) were taken from healthy, male, 8-12 weeks old rats (n=5, 200-250g) through cardiac puncture under general anesthesia into sterile EDTA containing tubes. Monocytes were separated by centrifugation and were resuspended in RPMI 1640 media (3.3±0.2x105 /ml). Cells were then incubated with metformin (2.5 µM, 25 µM, 250 µM) for 2,5 hours followed by addition of LPS (100 ng/ml, 1µg/ml) for further 5 hours. After centrifugation, the supernatant was taken and TNF-α level was measured by ELISA.

Results: There was no statistically significant change in the amounts of TNF-α in the LPS + metformin groups compared to the 100 ng/ml LPS group (p>0.05). In LPS+metformin groups, compared to 1 µg/ml LPS, 2.5 µM and 250 µM metformin significantly increased TNF-α levels (p<0.05), while 25 µM metformin did not make a significant difference (p>0.05). The amount of IL-6 was not within measurable range in this study.

Conclusion: In summary, metformin increased the amount of released TNF-α rather than decreased in our study.

Keywords: Metformin, Cytokine, LPS, Inflammation, Mononuclear Rat Cells

Sıçanlarda Lipopolisakkarid ile İndüklenen Monositlerde Metforminin TNF-α Salınımı Üzerine Etkileri

Araştırma Makalesi

Süreç

Geliş: 02/01/2024
Kabul: 22/01/2024

ÖZET

Amaç: İmmün sistem yanıtının bir sonucu olan inflamasyon, pek çok hastalıkta ortaya çıkan bir tablodur (ateroskleroz, hipertansiyon, diyabet, kanser, romatoid artrit gibi). Diyabet tedavisinde kullanılan metforminin, kan şekerini düzenleyici etkisinden bağımsız olarak, antienflamatuvar etkisininde olduğu bulunmuştur. Ancak etki mekanizması tam olarak açıklanamamıştır. Bu çalışmada, metforminin, lipopolisakkarit (LPS) ile inkübe edilmiş sıçan monositlerinden proinflamatuar sitokinler olan TNF-α ve IL-6 sentez ve salınımı üzerindeki etkisi araştırıldı.

Yöntem: Erkek 8-12 haftalık sağlıklı sıçanlardan (n=5, 200-250 g), genel anestezi (Xylazin 3 mg/kg + Ketamin 90 mg/kg) altında kardiyak puncture yöntemiyle 5 ml kan alındı ve steril EDTA'lı tüplere konuldu. Santrifuj (ficoll 3ml, 400xg, 30dk) yardımıyla mononükleer hücreler ayrıştırıldı. Hücreler RPMI 1640 media ile sulandırıldı (3.3±0.2x105 /ml). Hücreler önce metformin (2.5 µM, 25 µM, 250 µM) ile 2,5 saat inkübe edildi. Bu sürenin sonunda LPS (100 ng/ml, 1µg/ml) eklenerek 5 saat daha inkübe edildi. Daha sonra santrifuj (400xg, 20dk.) yapıldı, süpernatantlar -80°C'de, ELISA yöntemi ile TNF-α ve IL-6 düzeyleri ölçülene kadar saklandı.

Bulgular: Hücrelerin deneyler sonunda canlılık oranları %98'in üzerindeydi. TNF-α miktarları arasındaki fark, LPS 100 ng/ml ile, LPS + metformin (2.5µM, 25µM, 250µM) grupları karşılaştırıldığında (2179±359 ve 1613±437, 2915±572, 6059±948 pg/ml), istatistiksel olarak anlamlı bulunmadı (p>0.05). LPS 1µgr/ml ile, LPS+metformin (2,5µM, 25µM, 250µM) grupları karşılaştırıldığında (1752±553 ve 3023±745, 2344±598, 6238±841 pg/ml), 2.5µM (p0.05). IL-6 miktarları ELISA yöntemi ile ölçülecek miktarda bulunmadı. Bu konuda yapılan diğer çalışmalardan elde edilen sonuçlara göre, metforminin proinflamatuar sitokinlerin sentezini inhibe ettiği bulunmuştur.

Sonuç: Bu çalışmada, metformin, LPS ile indüklenen sıçan mononükleer hücrelerinden, TNF-α sentez ve salınımını, azaltmaktan ziyade artırmaya yönelik bir etki gösterdi.

Anahtar Kelimeler: Metformin, Sitokin, Lipopolisakkarit, Inflamasyon, Mononükleer Sıçan Hücresi

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How to Cite: Gedikli E, Parlak M, Soydan S. Effects Of Metformın On Tnf-A Release In Lıpopolysaccharıde-Induced Monocytes In Rats, Cumhuriyet Medical Journal. 2024;46(1):29-34

Introduction

Inflammation is a tissue caused by physical, chemical and other factors (pathogens). It is a strong physiological response at the cellular and humoral level to cellular injury. The aim in inflammation is to eliminate the damaging factor and products, to remove the harmful confined to the ground, repair of damaged tissues and to ensure its renewal.[1] The chemical mediator mediating the inflammatory tissue response is histamine. Discoveries of these mediators are also increasing. Mediators are various chemical substances that originate from damaged tissue, cells or plasma. In addition to histamine, chemicals such as substance P, serotonin, nitric oxide and cytokines are among the mediators that play a role in inflammation. Some intermediates are involved in inflammation (eg cyclooxygenase products). Some endogenous chemical mediators are released from the area of injury. These substances, called cytokines, are molecules in the protein structure.[2] Cytokines are in polypeptide structure and the most important ones in inflammation are interleukins (IL) and tumor necrosis factor-alpha (TNF-α). In particular, IL-6 and TNF-α share many common biological properties. Both are synthesized by activated macrophages, lymphocytes and other cell types and are called proinflammatory cytokines.[3] The molecular weight of the mature form of IL-6, which is a multifunctional cytokine, varies between 22000-30000kDa and consists of 184 amino acids.[4,5] The IL-6 gene is on chromosome.[7] Mononuclear phagocytic cells are the most important source of IL-6. IL-6 is also synthesized by fibroblasts, endothelial cells, B and T lymphocytes, hepatocytes, keratinocytes, glial cells, and bone marrow stroma cells.[6] IL-6 plays an important role in the defense mechanism of the host by regulating the immune response, acute phase reactions and hematopoiesis.[4,7,8] TNF, IL-1, platelet-derived growth factor (PDGF), cytokines such as IFN-beta, antigens, mitogens and bacterial endotoxins (lipopolysaccharide) stimulate IL-6 formation in different cell types. IL-6 is an important mediator of the inflammatory response. Cells involved in host defense against infectious microorganisms and their products and secreted by damaged tissues. IL-6 and TNF alpha levels were found to be high in sepsis and especially in septic shock caused by Gram(-) bacteria.[5,9] IL-6 concentration is increased in bacterial meningitis, CSF and blood.[10,11] It has been shown that IL-6 is released from monocytes in HIV infection. During infection some cytokines affect each other. IL-1 and TNF directly affect the IL-6 gene and increase the production of IL-6.[12] Although IL-6 has antiviral activity, it stimulates the production of MHC1 class antigens with interferons.[13] Tumor necrosis factor alpha (TNF-α) is a cytokine mainly synthesized by T lymphocytes and macrophages, with a secretory form of 17 KD and a membrane form of 26 KD.[14,15] TNF-α is a potent paracrine and autocrine regulator that acts locally at low concentrations (10-9 M) in immunoinflammatory reactions. It also regulates growth and differentiation in many cell types. Especially its combination with interferon-gamma (IFN-γ) is cytotoxic. It is involved in necrosis of murine sarcomas in vivo. Studies show that TNF-α plays an important role in acute inflammation and antitumoral immunity. It manages adhesion and chemotaxis by stimulating neutrophil and endothelial cells. TNF-α is secreted from many cell types such as activated monocytes, macrophages and, to a lesser extent, activated T cells, B cells, mast cells, fibroblasts, keratinocytes, Kupffer cells, smooth muscle, synovial cover cells, and basophils. TNF-α-mediated proliferation of fibroblasts and endothelial cells is important in wound healing. In addition, TNF-α is an important stimulant in the synthesis of endothelial vascular cell adhesion molecule (VCAM). TNF-α production is inhibited by IL-10, TGF-β, PGE, cyclosporine A, dexamethasone, ibuprofen, methylprednisolone and pentoxifylline.[16,17]

Metformin (C(=NH)NHC(=NH)N(CH3)2HCl) is a biguanide derivative oral antidiabetic with a molecular weight of 165.62. Metformin is slowly absorbed from the gastrointestinal tract after oral administration. It is mainly absorbed from the small intestine. Foods reduce the absorption of metformin and prolong its absorption time. The absolute bioavailability of the drug is approximately 50-60% and metformin reaching its peak plasma concentration in 1 - 3 hours following oral administration. Its binding to plasma proteins is negligible. Depending on time, it also enters into erythrocytes. It reaches steady-state plasma concentrations within 24-48 hours. Metformin is not metabolized in the liver. 90% of the absorbed drug is excreted within the first 24 hours mainly by tubular secretion and urinary tract. The half-life is about 1.5 - 6 hours. Metformin pharmacokinetics are not altered in diabetic and nondiabetic subjects with normal renal function at clinical doses. In patients with impaired renal function, the plasma and blood half-life of metformin is prolonged. It decreases glucose production in the liver, decreases the absorption of glucose from the intestines, and increases insulin sensitivity (increases peripheral glucose uptake and use).[18] While fasting insulin levels and all-day plasma insulin response increase with metformin treatment, insulin secretion is not stimulated. Its mechanism of action is different from other oral antidiabetic agents. Since metformin does not stimulate insulin secretion, unlike sulfonylureas, it does not cause hypoglycemia or hyperinsulinemia either in patients with type 2 diabetes or in normal individuals. During metformin treatment, fasting insulin levels and all-day plasma insulin response increase, and insulin secretion does not change.[19] Metformin has positive effects on abnormal serum lipid levels in most type II diabetic patients. Metformin alone or in combination with a sulfonylurea reduces mean fasting serum triglyceride, total cholesterol and LDL cholesterol levels without adverse effects on other lipid levels.[20] Gram-negative bacteria are bacteria that do not retain the crystal violet stain during the Gram staining procedure. Many Gram-negative bacteria are pathogenic. That is, they have the ability to cause disease in humans. This disease-causing ability is mainly due to the lipopolysaccharide (LPS) content of the Gram-negative cell

wall. In vivo, gram-negative bacteria, externally added LPS, or other endotoxins elicit a series of immune system responses. The most studied toxin is LPS in gram negative bacteria. Lipid A component in the LPS structure is responsible for toxicity.[21] This antigenic structure and toxins stimulate circulating mononuclear phagocytic cells by binding to the CD14 receptor. Tumor necrosis factor (TNF-α), interleukin and platelet-activating factor (PAF) are released from monocytes.[21] In this study, in order to investigate whether metformin has anti-inflammatory activity, the effect of metformin on the release of cytokines (TNF-α and IL-6) from LPS stimulated rat monocytes was investigated.

Materials and Methods

Animals and Drugs

In the research, Male 200–250 g, 8–12 weeks old healthy rats were used and left to normal water and feeding in 12 hours light and 12 hours dark environment. Experiment protocols were approved by Sivas Cumhuriyet University Animal Ethics Committee. The animals were habituated to laboratory conditions prior to testing. All experiments were performed blindly between 10 and 15 hours. PBS (phosphate buffer saline), RPMI 1640 media (Sigma-Aldrich), Ficoll Histopaque 1083 (Sigma-Aldrich), E. Coli 0111:B4 lipopolysaccharide (LPS), Metformin HCL (Bilim Pharmaceutical Factory, Turkey), TNF- α rat ELISA were used in the study. Metformin used in the research was from Bilim Pharmaceuticals; LPS was obtained from sigma company, TNF-α kit was obtained from RayBio. Rats were obtained from Cumhuriyet University animal laboratory.

Protocol

Rats were anesthetized with xylazine + ketamine (xylazine 3 mg/kg subcutaneous, ketamine 90 mg/kg subcutaneous), blood samples were taken by cardiac puncture method and placed in sterile EDTA tubes with a 10 ml sterile EDTA syringe. Blood samples taken from rats were placed in sterile 15 ml tubes and diluted 1:1 with PBS. 3 ml of Ficoll histopaque was added to another 15 ml tube. Phosphate buffer saline and blood mixture were slowly added onto Ficoll histopaque without mixing, and centrifuged (400xg) for 20 minutes. The mononuclear cells that were clearly differentiated were transferred to a sterile 15 ml centrifuge tube with the help of a pasteur pipette and 10 ml of PBS was added. Cells were washed by gentle shaking. It was centrifuged for 10 minutes (100xg), the supernatant was discarded, washing was repeated by adding 10ml of PBS. After the second wash, the cells remaining at the bottom were diluted with RPMI 1640 media (10 ml) in which 2.5 U heparin, 100 U penicillin, 100 µg streptomycin. A 1 ml sample taken from the cell stock was spread on Thoma slide and counted under 10x magnification. The sample taken in the same way was examined morphologically and the definition of mononuclear cells was provided. Giemsa and Liscia - De Marchi staining methods were used to define the cells morphologically. The cells were spread on the slide and covered with a coverslip, stained using 1µl Trypan Blue from the space between the coverslip and their viability was examined under the microscope. Cells with disrupted cell membrane structure appeared in blue. Lipopolysaccharide (LPS) was prepared as 100 ng/ml and 1 µg/ml in 0.9% saline. Metformin was prepared as 2.5 µM, 25 µM, 250 µM in 0.9% saline. The prepared solutions were sterilized with 2-micron diameter injector filters.

Incubation of Cells with LPS and Metformin

Cells were taken into 10 eppendorf tubes (20 - 40x10^4 cells/ml) and the tubes were incubated in the incubator (Nuaire, NU 5500E, USA) with LPS and/or Metformin as indicated below in the Table 1.

In accordance with this protocol, cells were first incubated with metformin for 2.5 hours. At the end of this period, LPS was added and incubated for another 5 hours. At the end of the incubation period, all Eppendorf tubes were centrifuged for 20 minutes in a micro-centrifuge device (Sigma, 6-16K, Germany). (400xg). Supernatants were taken and stored at –80 ºC until ELISA was performed. TNF-α levels were measured using the ELISA kit (RayBiotech Inc. USA). Micro plate reader (450nM wavelength selected) was used in the measurement.

Table 1 The experimental groups

Groups	Drugs
1	Carrier only (20 µl sterile 0.9% saline)
2	Carriers and 100 ng LPS (1 ml)
3	Carriers and 1 µg LPS (1ml)
4	100ng LPS and 2.5 µM Metformin
5	100 ng LPS and 25 µM Metformin
6	100ng LPS and 250 µM Metformin
7	1 µg LPS and 2.5 µM Metformin
8	1µg LPS and 25 µM Metformin
9	1 µg LPS and 250 µM Metformin
10	Carrier and 250 µM Metformin were added

Statistics

Results were evaluated using the Student-T (paired) test (SPSS 14.0 for Windows). P<0.05 value was considered statistically significant.

Result and Discussion

Control of Cell Viability

To check the viability of the cells, the cells were spread on the slide, covered with a coverslip, and the slide was stained using 1µl Trypan Blue from the gap between the coverslips, and their viability was examined under the microscope. Cells with disrupted cell membrane structure appeared in blue color. Viability rates were found to be >98%.

The Effect of Metformin on TNF- α Levels

When 100 ng/ml LPS (2179±359 pg/ml) was compared with LPS + metformin (2.5µM, 25µM, and 250µM) (1613±437, 2915±57, 6059±948 pg/ml respectively), the difference between them was not statistically significant (p>0.05) (Table 2, figure 1). On the other hand, metformin did not affect TNF-α amounts when given alone.

Table 2. Amounts of TNF-α (pg/ml) released from mononuclear cells under the influence of LPS (100ng/ml) and LPS + Metformin (2.5, 25, 250µM)

LPS (100ng/ml) (n=5)	**LPS+Met** (2.5µM) (n=5)	**LPS+Met** (25µM) (n=5)	**LPS+Met**(250µM) (n=3)
TNF-α (pg/ml) 2179±359	TNF-α (pg/ml) 1613±437	TNF-α (pg/ml) 2915±572	TNF-α (pg/ml) 6059±948
p value	p>0.05	p>0.05	p>0.05

Mean± standard error, p values compared to LPS 100ng/ml. Met: Metformin, LPS: Lipopolysaccharide, V: Carrier

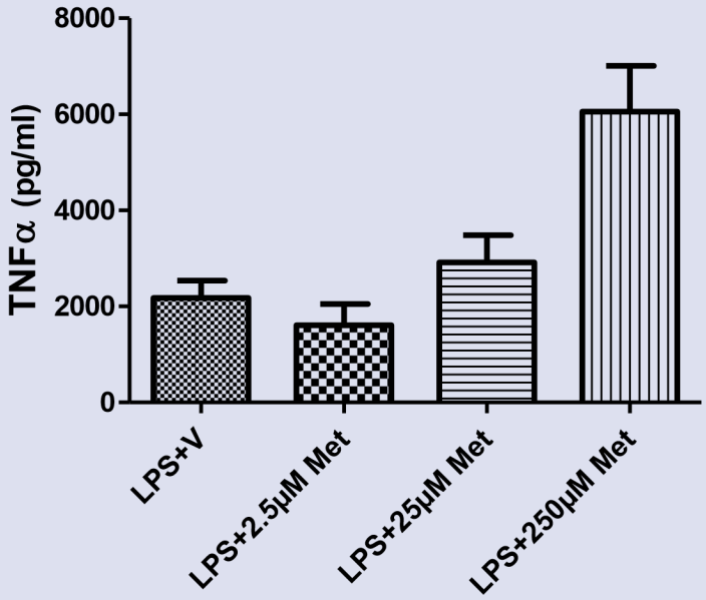

Figure 1: Amounts of TNF-α released from LPS (100 ng/ml)-induced mononuclear cells via LPS and LPS + Metformin (2.5, 25, 250µM) (pg/ml, mean±standard error). Met: Metformin, LPS: lipopolysaccharide, V: Carrier

Table 3:. Amounts of TNF-α (pg/ml) released from mononuclear cells under the influence of LPS (1µg/ml) and LPS + Metformin (2.5, 25, 250µM)

LPS (1µgr/ml) (n=5)	**LPS+Met** (2.5 µM) (n=5)	**LPS+Met** (25µM) (n=5)	**LPS+Met** (250µM) (n=5)
1752±553	3023±745	2344±598	6238±841
p value	p<0.05	p>0.05	p<0.05

Mean± standard error, p values compared to LPS 100ng/ml. Met: Metformin, LPS: Lipopolysaccharide, V: Carrier

When 1µg/ml LPS (1752±553 pg/ml) was compared to LPS + metformin (2.5µM, 25µM, and 250µM) (3023±745, 2344±598, and 6238±841 pg/ml respectively), metformin at doses of 2.5 µM and 250 µM (p<0.05) significantly increased TNF-α levels, while metformin at dose of 25 µM did not make a difference (p>0.05) (Table 3, figure 2). On the other hand, metformin did not affect TNF-α amounts when given alone.

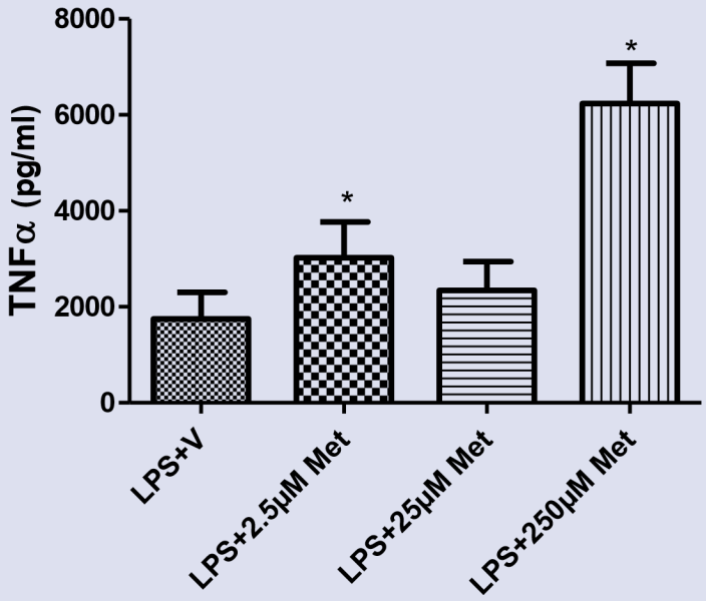

Figure 2: Amounts of TNF-α released from LPS (1μg/ml)-induced mononuclear cells via LPS and LPS + Metformin (2.5, 25, 250μM) (pg/ml, mean±standard error). Met: Metformin, LPS: lipopolysaccharide, V: Carrier

The Effect of Metformin on IL-6 Levels

The amounts of IL-6 were not measurable in all experiments.

The anti-inflammatory effects of metformin have been examined in liver, lung, endothelial cells, and macrophages in many studies. This study shows that metformin reduces liver triglyceride content in fat-rich fed rats and its anti-inflammatory effect is confirmed by the decrease in the amount of TNF-α and MMPs activity.[22] Additionally, it has been stated that metformin has an effect on improving liver dysfunction after partial hepatectomy, preventing neutrophil accumulation in the liver, and preventing the increase of IL-6 and interferon-γ.[21]

Studies in animal models reveal that metformin reduces hepatic inflammation in non-alcoholic steatohepatitis models and has an anti-inflammatory effect in conditions such as acute lung injury.[23,24,25] However, the effect of metformin on reducing the amount of TNF-α in the experiment conducted in this study differed from similar studies in the literature. It has been emphasized that high metformin concentrations may cause toxic effects and therefore should be used with caution. Although the results of the study differ from similar studies in the literature, it was emphasized that these differences may be due to factors such as species differences, experimental conditions and metformin concentrations used. At this point, the importance of studies evaluating the anti-inflammatory effects of metformin, especially at the doses used in clinical applications in humans, is emphasized. In addition to metformin's effects on glucose metabolism, the study noted that it reduced plasminogen activator inhibitor (PAI)-1, von-Willebrand factor, and smooth muscle cell contractility, and reduced inflammation markers in cases of polycystic ovary syndrome. These findings suggest that metformin may play a positive role not only in the treatment of diabetes but also in the modulation of inflammation. It has been stated that metformin increases AMP-mediated activated protein kinase (AMPK) activity and thus reduces the release of pro-inflammatory agents. This effect supports the idea that metformin may also be effective as an antiatherogenic drug in diabetic patients. According to the results of the study, the effect of metformin on reducing or increasing TNF-α release from rat mononuclear cells differed from similar studies in the literature. This difference may be due to differences in the cell type used, experimental conditions, and metformin concentrations. Therefore, it has been emphasized that in studies evaluating the anti-inflammatory effects of metformin, it is important to carefully select the species and experimental conditions.

Conclusion

At concentrations of 2.5 and 250 μM, Metformin exhibited an augmentation in the released TNF-α levels instead of a reduction, despite the induction being carried out with 1 μgr/ml LPS.

Conflict of Interest

Authors declare no conflict of interest.

Acknowledgement

The authors would like to thank the Sivas Cumhuriyet University, School of Medicine, CUTFAM Research Center, Sivas, Turkey, for providing the necessary facilities to conduct this study.

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CMJ. 2024;46(1):35-40
DOI: 10.7197/cmj.1414749

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Living with Family and Clinical, Demographic, and Laboratory Characteristics in Patients with Heart Failure

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Research Article

History

Received: 05/01/2024
Accepted: 04/03/2024

ABSTRACT

Objective: Heart failure (HF) is a progressive clinical syndrome associated with significant morbidity and mortality. It is known that during the course of this syndrome, social factors can impact clinical outcomes alongside medical interventions. Studies have demonstrated that social support provides favorable developments in mortality rates, event-free survival, and readmission rates in HF patients. In our study, we aimed to elucidate the effects of the concept of family, the most significant social support, on clinical characteristics, exercise capacity, echocardiographic, and laboratory features in HF cases.
Methods: A multicenter cohort study was conducted, including 303 patients previously diagnosed with HF, following current guidelines and presenting for outpatient follow-up. Patients with a new diagnosis of HF, those with acute decompensated HF, and those with a history of malignancy were excluded from the study. Demographic data (age, gender), comorbidities (hypertension, diabetes mellitus, atrial fibrillation, etc.), HF treatments, laboratory tests, and detailed transthoracic echocardiography results were recorded.
Results: Patients were divided into two groups based on whether they lived with a spouse, parent, child, or without any of them, defining the presence or absence of family support. In the study, 303 patients with an average age of 62.1±13.0, of which 94 (31%) were female, were included. The mean left ventricular ejection fraction was 28.7±8.1. When the groups were compared in terms of comorbidities, there was no statistically significant difference in the presence of hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, stroke, or atrial fibrillation (all p>0.005). Coronary artery disease was more frequently observed in the group with family support, while chronic kidney disease was more common in the group without family support (p=0.008 and p=0.012, respectively). Smoking prevalence was significantly higher in the group without family support, while alcohol use showed no significant difference (p=0.046 and p=0.602, respectively). Analyzing the results, it was observed that patients with family support were more regularly monitored for HF reasons (71% vs. 59%, p=0.054).
Conclusion: It has been observed that the social support provided by family members in individuals with HF can have positive effects on the clinical course of the disease and the patient's lifestyle.

Keywords: Heart failure, Family, Social support

Kalp Yetersizliği Hastalarında Aileyle Birlikte Yaşamanın Hastalığın Klinik, Demografik ve Laboratuvar Özellikleriyle İlişkisi

Süreç

Geliş: 05/01/2024
Kabul: 04/03/2024

ÖZET

Amaç: Kalp yetersizliği (KY) ciddi morbidite ve mortalite ile seyredebilen ilerleyici klinik bir sendromdur. KY seyri sırasında tıbbi müdahalelerin yanı sıra, sosyal faktörlerin de klinik sonuçları etkileyebileceği bilinmektedir. Sosyal desteğin KY hastalarında mortalite, olaysız sağ kalım ve yeniden yatış oranlarında tatmin edici gelişmeler sağladığı gösterilmiştir Biz de çalışmamızda en büyük sosyal destekleyici olan aile kavramının KY olgularında klinik özellikler, egzersiz kapasitesi, ekokardiyografik ve laboratuar özellikleri üzerine olan etkilerini ortaya koymayı amaçladık.
Yöntem: Çok merkezli, kesitsel olarak yapılan çalışmaya güncel kılavuzlara uygun olarak daha önce KY tanısı koyulan ve ayaktan takip amacıyla poliklinik başvurusu olan 303 hasta dahil edildi. Yeni tanı KY, akut dekompanse KY olan hastalar ile malignite öyküsü olanlar çalışmadan dışlandı. Hastaların demografik verileri (yaş, cinsiyet), komorbiditeler (hipertansiyon, diabetes mellitus, atriyal fibrilasyon vb.), kullandıkları KY tedavileri, laboratuvar testleri ve ayrıntılı transtorasik ekokardiyografi sonuçları dahil olmak üzere ayrıntılı klinik verileri kaydedildi. Hastalar eş, anne, baba veya çocuklarıyla aynı evde yaşıyorsa aile desteği olanlar, bunlardan herhangi biri yoksa aile desteği olmayanlar şeklinde 2 gruba ayrılarak karşılaştırıldı.
Bulgular: Çalışmaya 94'ü (%31) kadın ve yaş ortalaması 62,1±13,0 olan 303 KY tanılı hasta dahil edildi. Hastaların ortalama sol ventrikül ejeksiyon fraksiyonu 28,7±8,1 idi. Gruplar komorbiditeler açısından karşılaştırıldığında hipertansiyon, diyabetes mellitus, hiperlipidemi, kronik obstruktif akciğer hastalığı, inme, atrial fibrilasyon varlığı açısından istatistiksel anlamlı fark yoktu (hepsi için, p>0.005). Koroner arter hastalığı aile desteği olan grupta anlamlı şekilde daha sık görülmekteyken kronik böbrek hastalığı ise aile desteği olmayan grupta daha sık izlenmekteydi. (sırasıyla p=0,008 ve p=0,012). Sigara kullanımı aile desteği olmayan grupta anlamlı şekilde daha yüksek iken alkol kullanım oranları arasında fark izlenmedi (sırasıyla p=0,046 ve p=0,602). Yapılan analizler sonunda aile desteği olan gruptaki hastaların KY nedeniyle daha yüksek oranda düzenli takipte olduğu görüldü (%71 vs. %59, p=0,054).
Sonuç: KY sahip kişilerde aile bireyleri tarafından oluşturulan sosyal desteğin hastalığın klinik seyri ve hastanın yaşam alışkanlıkları üzerine olumlu etkileri olabileceği görülmüştür.

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How to Cite: Şahin ET, Yılmaz Öztekin GM, Genç A, Şahin A. Living with Family and Clinical, Demographic, and Laboratory Characteristics in Patients with Heart Failure. Cumhuriyet Medical Journal. 2024;46(1): 35-40.

Introduction

Heart Failure (HF) is a significant clinical syndrome resulting from the heart's diminished efficiency and the inability of circulating blood to meet the body's needs due to pathological changes in the cardiovascular system [1]. It is a complex condition with diverse symptoms affecting around 60 million people globally, 2 million people in our country, posing a widespread health concern [2,3]. Established drug classes are available to mitigate mortality in HF; nevertheless, adherence to these medications and consistent follow-up are imperative [4].

Throughout the progression of HF, several factors influence patients' quality of life. Among these factors, the level of environmental support holds substantial importance. Social support plays a pivotal role in enhancing patients' coping mechanisms, supporting treatment adherence, and positively impacting overall clinical outcomes [5]. In this context, the family stands out as one of the most crucial sources of social support in an individual's life. Despite various sources of social support, having a spouse and continuous support is deemed one of the most effective for HF patients [6]. Research has demonstrated the positive effects of being married or living with a partner in reducing mortality rates, promoting event-free survival, and lowering readmission rates in HF patients [7,8]. Conversely, HF patients with inadequate or no social support have been associated with higher rates of readmission and mortality [9-11]. Reports indicate that marital status significantly influences outcomes in HF [12,13]. While studies on HF typically concentrate on spousal support, it is crucial to recognize the presence of other family members sharing the same household as additional sources of social support.

This study aims to comprehend the potential impacts of family support on clinical characteristics, exercise capacity, echocardiographic findings, and laboratory features in HF patients.

Material and Methods

A total of 303 patients, followed in the outpatient clinic between 2018-2020, were included in this multicenter observational cohort study investigating the impact of living with family on the course of HF. Ethics Committee Approval was received. The study complied with the Declaration of Helsinki and informed consent has been obtained from all participants.

In this study, when α=0.05, β=0.20, 1-β=0.80, it was decided to include 300 individuals in the study and the power of the test was found to be 0.83234.

Exclusion criteria for the study were patients with insufficient information about living with family, the presence of acute decompensated HF, and newly diagnosed HF.

Demographic information on patients, HF etiology, presence of comorbidities like hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD) chronic obstructive pulmonary disease (COPD), New York Heart Association (NYHA) functional class, drug usage informations, physical examination findings (height, weight, pulse, blood pressure), HF symptoms and signs, left ventricle ejection fraction (LVEF) and routine biochemical parameters (hemogram, sodium, potassium, creatinine, N-terminal–pro-brain natriuretic peptide [NT-proBNP], glomerular filtration rate [GFR]) values were collected.

Electrocardiogram (ECG) findings and medication details were retrieved from the hospital registry system. Transthoracic echocardiography (TTE) was performed with an EPIQ 7 (Koninklijke Philips NV, Amsterdam, the Netherlands) echocardiography device and a 1.5–4.5 MHz ultrasound probe following the American Society of Echocardiography Standards [14]. LVEF was measured using the Simpson method.

Information regarding the patient's family life was collected through face-to-face interviews. Patients were considered to be living with family if they shared the same household with family members. Patients were divided into two groups, those living with their family and those not living with their family, and analyses were conducted accordingly.

Statistical Analysis

Data were recorded in a collection form, and statistical analyses were performed using IBM SPSS software version 23. Descriptive statistics were presented with frequency (%), mean±standard deviation, and median (min-max). Normal distribution conformity was assessed using histogram graphics and the Kolmogorov-Smirnov test. The Mann-Whitney U test evaluated non-normally distributed variables (HF etiology, HF type, gender, presence of DM, HT, CKD and COPD). The correlation between living with family and correlation was examined using the Spearman's bivariate correlation method. Correlation coefficients and p-values were determined. A p value <0.05 was considered statistically significant.

Results

Out of the 303 patients included in our study, 238 (78.5%) reported having support from family members residing in the same household. The mean age of the included patients was 62.1±13.0 years. The average age of patients with family support was found to be lower compared to those without support (61.5±13.2 vs 64.5±11.9, p=0.512).

Among the enrolled patients, 94 (31%) were female, with a higher proportion of females observed in the group without family support (29% vs. 40%, p=0.078). The presence of CAD was more prevalent in the group with family support (61% vs. 43%). Demographic characteristics based on the presence of family support are detailed in Table 1.

Evaluation based on NYHA functional classes revealed that advanced stages (NYHA III-IV) were present in 39% (25 cases) of the group without family support, while this number was 26% (61 cases) in the group with family support. There were no statistically significant differences between the groups regarding the use of guideline-recommended beta-blockers (BB), SGLT-2 inhibitors, and mineralocorticoid receptor antagonists (MRA) (Table 2).

Table 1. Baseline demographic characteristics according to the presence or absence of family support in heart failure patients

	Total (n=303)	Family support presence (n=238)	Family support absence (n=65)	p Value
Age, years	62.1±13.0	61.5±13.2	64.5±11.9	0.512
Female, n (%)	94 (%31)	68 (%29)	26 (%40)	0.078
Body mass index, kg/m2	27.3±5.7	27.4±5.6	27.2±6.2	0.812
Hypertension, n (%)	162 (%54)	126 (%53)	36 (%55)	0.726
Diabetes mellitus, n (%)	122 (%40)	97 (%41)	25 (%39)	0.848
Atrial fibrillation, n (%)	54 (%18)	42 (%18)	12 (%19)	1.000
Coronary artery disease, n (%)	174 (%57)	146 (%61)	28 (%43)	0.008
COPD, n (%)	55 (%18)	46 (%19)	9 (%14)	0.404
Dyslipidemia, n (%)	134 (%44)	102 (%43)	32 (%49)	0.359
Ischaemic stroke, n (%)	33 (%11)	29 (%12)	2 (%6)	0.247
Chronic kidney disease, n (%)	43 (%14)	27 (%11)	16 (%25)	0.012
Smoking, n (%)	61 (%20)	42 (%18)	19 (%29)	0.046
Alcohol, n (%)	20 (%7)	15 (%7)	5 (%9)	0.602
Heart rate, bpm	79.3±17.5	78.4±17.3	82.8±17.6	0.073
Systolic blood pressure, mmHg	112.4±18.6	112.3±18.2	112.9±20.5	0.818
Diastolic blood pressure, mmHg	64.4±10.8	64.3±10.4	64.9±12.3	0.668
NYHA 3-4, n (%)	86 (%28)	61 (%26)	25 (%39)	0.060
Dietary complience, n (%)	200 (%66)	161 (%68)	39 (%60)	0.249
Regular follow-up, n (%)	207 (%68)	169 (%71)	38 (%59)	0.054

COPD: chronic obstructive pulmonary disease, NYHA: New York Heart Association functional capacity

Table 2. Laboratory and clinical characteristics according to the presence or absence of family support in heart failure patients

	Total (n=303)	Family support presence (n=238)	Family support absence (n=65)	p Value
Hemoglobin, g/dL	13.2±1.9	13.2±1.9	13.0±2.0	0.604
NT-proBNP, pg/mL	4126(2840-9179)	3447 (2840-4053)	6643 (4107-9179)	0.017
Sodium, mmol/L	138.6±3.8	138.7±3.9	138.1±3.4	0.296
Potassium, mmol/L	4.6±0.5	4.6±0.5	4.5±0.5	0.550
Albumin, g/dL	4.4±0.5	4.4±0.5	4.4±0.6	0.857
Creatinine, mg/dL	1.2±0.7	1.2±0.7	1.3±0.5	0.154
GFR, CKD-EPI	67.1±23.8	69.8±23.8	57.1±20.8	<0.001
LDL, mg/dl	105.8±45.8	106.3±45.7	103.8±46.5	0.695
LV ejection fraction, %	28.7±8.1	28.2±8.0	30.2±8.4	0.077
ACEi or ARB, n (%)	247 (%82)	202 (%85)	45 (%70)	0,007
ARNI, n (%)	16 (%5)	14 (%6)	2 (%3)	0.342
Beta blocker, n (%)	274 (%90)	218 (%92)	56 (%86)	0.278
MRA, n (%)	215 (%71)	169 (%71)	46 (%71)	1.000
Loop Diuretic, n (%)	194 (%64)	147 (%62)	47 (%72)	0.116
Thiazide, n (%)	76 (%25)	60 (%25)	16 (%25)	1.000
Digoxin, n (%)	30 (%10)	24 (%10)	6 (%9)	1.000
Ivabradine, n (%)	28 (%9)	23 (%10)	5 (%8)	0.807
SGLT-2 inh, n (%)	56 (%19)	47 (%20)	9 (%14)	0.365
Influenza vaccination, n (%)	42 (%14)	36 (%15)	6 (%9)	0.309
ICD, n (%)	33 (%11)	28 (%12)	5 (%8)	0.478

ACEi: anjiotensin converting enzim inhibitors, ARB: anjiyotensin reseptör blockers, ARNI: angiotensin receptor/neprilysin inhibitör, CRT: cardiac resynchronization therapy, ICD: implantable cardioverter defibrillator, LV: left ventricle, MRA: mineralocorticoid reseptör antagonist, NT-proBNP: N-terminal pro-brain natriuretic peptide, SGLT-2 inh: sodium-gucose transport protein 2 inhibitors

Table 3. Correlation between family support presence and demographic and clinical characteristics in patients with heart failure

Parameters	r Value	p Value
Sex, Female	0.101	0.780
Coronary artery disease	-0.152	0.008
Hypertension	0.103	0.073
Diabetes mellitus	0.019	0.739
Chronic kidney disease	-0.156	0.006
Ischemic stroke	0.079	0.168
Chronic obstructive pulmonary disease	0.058	0.311
Smoking	-0.199	0.039
Alcohol use	-0.033	0.595
Dietary complience	0.066	0.250
NYHA III-IV	-0.117	0.042
Influenza vaccination	0.070	0.224
Atrial fibrillation	-0.009	0.880
Implantable cardioverter defibrillator	0.054	0.352
Regular follow-up	0.111	0.045

NYHA: New York Heart Association

However, renin-angiotensin system inhibitor (RAS-i) usage was higher in the group with family support (85% vs. 70%, p=0.007).

When examining baseline laboratory characteristics, parameters other than NT-proBNP and GFR were similar in both groups (Table 2). In the group with family support, NT-proBNP values were lower, and GFR values were higher (Table 2).

Comparison between patient groups with and without family support revealed some differences in baseline characteristics (Table 1). Correlation analyses between the presence of family support and various parameters indicated a significant negative correlation with CAD, CKD, smoking, and the presence of advanced functional capacity. Conversely, a significant positive correlation was found between the presence of family support and regular follow-up for HF management (Table 3).

Discussion

This study explores the interaction between familial support and various dimensions of HF patients, including clinical characteristics, exercise capacity, echocardiographic findings, and laboratory features. The high prevalence of familial support reported in 78.5% of HF patients underscores the crucial role familial dynamics play in the lives of individuals grappling with this chronic condition. However, this rate may be influenced by cultural and geographical differences. The findings align with existing study data investigating familial support among individuals with chronic illnesses in our country [15]. The patients included in our study are relatively younger, considering the average age of HF in our country. The tendency for the group with familial support to be younger suggests that family cohesion might be more easily maintained at early ages. As individuals age, family support may diminish due to various factors. Additionally, our study reveals that females experience less familial support, consistent with studies indicating that women benefit less from social support in societies. The gender-specific aspects of familial care in individuals with chronic illnesses may vary between communities and cultures. According to our study, men with HF seem to have more familial support than women. A more detailed examination of the gender-familial support relationship may help understand the challenges faced by female HF patients lacking robust familial networks.

No clear relationship is observed between comorbidities and familial support in HF patients. However, CAD tends to be more prevalent in individuals with familial support. This might imply a higher post-CAD survival rate in those with familial support, but further studies are needed to establish causality.

The NYHA functional classification plays a significant role in both the diagnostic process and treatment management of HF patients [16]. The higher prevalence of advanced stages (NYHA III-IV) in the group without familial support may indicate the potential impact of social dynamics on disease progression. Individuals without family support seem to have more uncontrolled and risky conditions regarding HF. This aligns with studies focusing on HF based on marital status.

Our study's HF patients adhere to medical treatments under expert guidance. Usage rates, especially when compared to European-based registry studies, are higher in our study [17,18]. However, there is no statistical significance in the usage of medications recommended by guidelines between the two groups. This suggests that, despite receiving similar optimal treatments, the group without familial support may experience worse functional capacity due to social factors. It is crucial to recognize that HF treatment cannot solely rely on medications, and the presence of social support may play a crucial role in achieving therapeutic goals.

Similarly, NT-proBNP values, indicative of HF severity, are essential markers in HF patients [19]. In the group without familial support, elevated levels of natriuretic peptides despite optimal treatment suggest inadequate control of disease severity.

The interaction between the kidneys and the heart is vital, particularly in HF patients [20]. Although the average GFR values in our study align with previous large-scale HF studies, significantly lower GFR values in the group without familial support may imply a higher prognostic risk in these patients [21]. However, more comprehensive studies are required to understand the mechanisms behind these findings and their clinical implications.

Smoking is an independent risk factor for cardiovascular disease and mortality [22]. Our study reveals higher smoking rates in individuals with HF lacking familial support. This may be associated with both insufficient social support and worse clinical conditions in terms of HF.

While no significant difference is detected in dietary compliance based on familial support in HF patients, a positive correlation is found between regular follow-up and familial support. This suggests that the concept of family may motivate individuals to monitor their illnesses more diligently.

Despite numerous studies assessing the impact of self-care, marital status, and the social environment on HF patients, our study stands out by specifically evaluating the presence of family members sharing the same household [9,10,23]. It highlights the role of social supporters living with HF patients, such as spouses, children, or parents. Existing studies present conflicting results regarding the impact of being married on HF outcomes, with some reporting no effect, while others suggest worse outcomes, especially in individuals who have been married and divorced [24,25]. Our study contributes to this body of knowledge by emphasizing that not only major outcomes like death, but also functional capacity and quality of life are crucial treatment goals for HF patients.

Our study has some limitations. Firstly, the relatively small number of patients and the single-center collection of data limit the generalizability of the findings. Additionally, variations among researchers in obtaining data pose another limitation. As the LVEF of the patients in our study is ≤40%, there is insufficient data for HF patient groups with mildly reduced and preserved EF. Moreover, familial support in our study is defined as the presence of family members sharing the same household, and the specific impact of family members on providing social support is not thoroughly evaluated. Due to these limitations, larger, prospective, multicenter studies are needed in the future.

Conclusion

In conclusion, this study provides valuable data on the complex relationship between familial support and various aspects of HF. The findings highlight the positive impact of the presence of familial support on the management and clinical outcomes of HF patients. As a result of this study, there arises a need for future research to evaluate the relationships between familial support and HF outcomes over a longer term.

Declaration Of Interests

The authors declare no conflicting interests.

Acknowledgements

None.

Funding

None.

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CMJ. 2024;46(1):41-44
DOI: 10.7197/cmj.1415665

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Determination of the Percentage of Patients Using Warfarin to Reach Target INR

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Research Article

History

Received: 06/01/2024
Accepted: 07/03/2024

ABSTRACT

Objective: Warfarin is the most commonly used oral anticoagulant in the treatment and prophylaxis of thromboembolic diseases. In order to prevent thrombosis and to avoid hemorrhagic complications, the patient's International Normalized Ratio (INR) is kept within a certain range according to the indication and monitored at certain intervals. Our aim in our study is to determine the percentage of patients using warfarin for various indications reaching target INR values.
Methods: Patients who used warfarin for various indications at our hospital's Internal Medicine outpatient clinic between May 2023 and November 2023 were included in our study, and their INR results were recorded by retrospectively scanning them.
Results: A study group was formed with a total of 130 patients. Patients using warfarin due to metallic heart valve replacement, AF, PTE and CVD were evaluated separately according to the target INR value. The percentage of patients with metallic heart valve replacement reaching the target INR value of 2.5-3.5 was calculated as 38.5% (n: 27). The percentages of patients with AF, PTE and CVD reaching their target INR values of 2-3 were calculated as 40% (n:16), 54% (n:7), 70% (n:5), respectively. Considering the entire study group, the percentage of reaching the target INR was calculated as 42% (n: 55).
Conclusion: As a result, warfarin not being within the therapeutic range causes serious morbidity and mortality. In our study, the percentage of patients reaching the target INR was found to be 42%. This percentage is very low, and in order to increase this rate, it is necessary to increase patient awareness, increase the frequency of follow-up of patients and develop more effective follow-up strategies.

Keywords: Warfarin, INR, Thrombosis, Bleeding

Varfarin Kullanan Hastaların Hedef INR'ye Ulaşma Yüzdesinin Belirlenmesi

Araştırma Makalesi

Süreç

Geliş: 06/01/2024
Kabul: 07/03/2024

ÖZET

Amaç: Varfarin tromboembolik hastalıkların tedavisinde ve profilaksisinde en sık kullanılan oral antikoagülandır. Trombozun oluşmasını engellerken aynı zamanda hemorajik komplikasyonlardan kaçınmak için hastanın Uluslararası Normalleştirilmiş Oranı (INR) endikasyonuna göre belirli aralıkta tutulur ve belirli aralıklarla takip edilir. Bizim çalışmamızdaki amacımız çeşitli endikasyonlarda varfarin kullanan hastaların hedef INR değerlerine ulaşma yüzdesinin saptanmasıdır.
Yöntem: Çalışmamıza hastanemize Mayıs 2023 ile Kasım 2023 tarihleri arasında İç Hastalıkları polikliniğine çeşitli endikasyonlar sebebiyle varfarin kullanan hastalar dahil edilmiş ve retrospektif olarak taranarak INR sonuçları kayıt altına alınmıştır.
Bulgular: Toplam 130 hasta ile çalışma grubu oluşturulmuştur. Metalik kalp kapak replasmanı, AF, PTE ve SVH nedeniyle varfarin kullanan hastalar ayrı ayrı hedef INR değerine göre değerlendirilmiştir. Metalik kalp kapak replasmanlı hastaların hedef INR'ye ulaşma yüzdesi %38,5 (n: 27) olarak, AF, PTE ve SVH'li hastaların hedef INR'lerine ulaşma yüzdeleri sırasıyla %40 (n:16), %54 (n:7), %70 (n:5) olarak tespit edildi. Tüm çalışma grubu göz önüne alındığında ise hedef INR'ye ulaşma yüzdesi %42 (n:55) olarak hesaplandı.
Sonuç: Sonuç olarak varfarinin terapötik aralıkta bulunmaması ciddi morbitide ve mortaliteye yol açmaktadır. Çalışmamızda hedef INR'ye ulaşan hasta yüzdesi %42 olarak saptanmıştır. Bu yüzde çok düşük olup, bu oranı artırmak için hasta farkındalığının artırılması, hastaların takip sıklığının artırılması ve daha etkili takip stratejileri geliştirilmesi gerekmektedir.

Anahtar Kelimeler: Varfarin, INR, Kanama, Tromboz

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How to Cite: Keskin Z, Gedikli MA. Determination of the Percentage of Patients Using Warfarin to Reach Target INR. Cumhuriyet Medical Journal. 2024;46(1):41-44

Introduction

Warfarin, a vitamin K antagonist, is used as an oral anticoagulant for primary and secondary antithrombotic prophylaxis.[1] The anticoagulant effect of warfarin is due to its structural similarity to vitamin K. It achieves this effect by inhibiting vitamin K epoxide reductase, the enzyme that converts vitamin K epoxide back into vitamin K. Thus, an anticoagulant effect is achieved by reducing the amount of active vitamin K available for the activation of clotting factors II, VII, IX and X.[2] The anticoagulation effectiveness of vitamin K antagonists is monitored by the international normalized ratio (INR). The INR is kept within a determined therapeutic range for the balance between preventing thromboembolic events and preventing hemorrhagic complications.[3] In diseases such as atrial fibrillation (AF) and venous thromboembolism (VTE), the INR is targeted to be 2-3. Many high-quality randomized studies have shown that aiming for a lower INR target range, such as 1.5-2, provides inadequate protection against thromboembolism without any reduction in major bleeding rates.[4] In addition, patients with mechanical heart valves must use anticoagulants for life to protect themselves from thromboembolic complications. Considering the patient's valve and risk status, the INR value is desired to be between 2.5-3.5. Therefore, clinically stable patients are usually monitored with INR every 4-6 weeks, and unstable patients are monitored with INR at shorter intervals such as every week or every few days.[5] Studies have shown that even patients with very careful and optimal follow-up have difficulty reaching therapeutic INR. The reasons for this difficulty in reaching the target INR are many actors have been shown, such as inadequate compliance with warfarin treatment, irregularity in dietary vitamin K intake, interaction with other drugs, and genetic differences between patients.[6]

Our study aimed to determine the percentage of patients using warfarin for various indications reaching target INR values.

Material and Method

In our study, the INR results of patients who came to our hospital for INR monitoring due to warfarin use at the Internal Medicine outpatient clinic between May 2023 and November 2023 were scanned using the hospital information management system Ethics committee approval was obtained before the study. Patients using warfarin due to indications such as metallic heart valve replacement, AF, cerebrovascular disease (CVD), pulmonary embolism (PTE) were included in our study. The patients included in the study were selected from patients using warfarin for more than 6 months and were recorded based on the last INR value during follow-up. A study group was formed with 130 patients who met these criteria.

Previously studied INR results due to warfarin use were scanned and recorded. Target INR value of the patients included in the study; It was evaluated as 2.5-3.5 in patients with mechanical prosthetic valves, and as 2.0-3.0 in patients with AF, PTE, deep vein thrombosis and CVD. Then, the percentages of patients whose results were at the target INR value were calculated according to the indication for warfarin use. Analysis of study data was performed using Statistical Package for Social Sciences (SPSS) software, Version 25.0 (Armonk, NY: IBM Corp.) on Mac OS. Demographic and clinical characteristics of the participants were examined with descriptive statistical analyzes such as numerical, percentage, mean and standard deviation. Chi-square test was used to evaluate the relationship between categorical variables. The Kolmogorov-Smirnov test was preferred to determine the suitability of the data for normal distribution. Independent samples t test was applied to evaluate the difference between independent variables that were suitable for normal distribution. $p<0.05$ was considered significant.

Results

130 patients who were followed up due to warfarin use in the Internal Medicine outpatient clinic were included in the study. While 54% (n:70) of these patients were women, 46% (n:60) were men. The average age was calculated as 63.93±12.78 (range 20-90). The average INR of the study group was determined as 3.15±1.31 (1.4-9.81 INR range). Indications for warfarin use in the patients included in the study were metallic heart valve replacement, AF, CVD and PTE. The number of patients and percentages of these indications are shown in Table 1.

The percentage of patients with metallic heart valve replacement reaching the target INR value of 2.5-3.5 was calculated as 38.5% (n: 27). The percentages of patients with AF, PTE and CVD reaching their target INR values of 2-3 were calculated as 40% (n:16), 54% (n:7), 70% (n:5), respectively. Considering the entire study group, the percentage of reaching the target INR was calculated as 42% (n: 55). The percentages of reaching the target INR by indication and the percentages of patients with subtherapeutic and supratherapeutic INR are shown in Table 2.

No statistically significant difference was detected in reaching the target INR according to the indications. ($p > 0.05$)

Table 1. Percentages and numbers of patients using warfarin according to indication

Indication	%	Number (n)
Metallic Heart Valve Replacement	54	70
AF	30.7	40
PTE	10	13
CVD	5.3	7

Table 2. Percentages of reaching target INR by indication

Indication	Target INR	Subtherapeutics	Supratherapeutics
Metallic Heart Valve Replacement	38.5% (n:27)	33% (n: 23)	28.5% (n:20)
AF	40% (n:16)	15% (n:6)	45% (n:18)
PTE	54% (n:7)	8% (n:1)	38% (n:5)
CVD	70% (n:5)	15% (n:1)	15% (n:1)
Total	42% (n:55)	24% (n:31)	34% (n:44)

Discussion

Warfarin is the most commonly used oral anticoagulant in the treatment and prophylaxis of thromboembolic diseases. In order to prevent thrombosis and to avoid hemorrhagic complications, the patient's INR should be kept within a certain range according to the indication. Therefore, warfarin has a narrow therapeutic range and the drug has a complex dose-response relationship that makes safe and effective use difficult. Considering the interactions of warfarin with other drugs and foods and genetic differences, careful INR monitoring and treatment management are required, especially in elderly patients.[7]

In a multicenter, prospective study with 4987 patients, patients using warfarin for various indications were included in the study and the awareness of these patients, time in therapeutic range (TTR) and safety of warfarin treatment were investigated. The indications for using warfarin were mechanical valve in 42.6%, AF in 38.4%, and other warfarin indications in 19%. It was observed that awareness of warfarin decreased in older age groups, and it was determined that only patients with knowledge about food-drug interactions of warfarin constituted 55% of the study group. People with higher warfarin awareness were observed to have higher TTR levels. In this study, 70.9% of INRs were above the therapeutic range, 24.6% were in the therapeutic range, and 4.6% were below the therapeutic range. As a result of the study, the patients' average TTR rates and awareness of warfarin treatment were found to be low, and it was thought that the reason for the low TTR might be due to food-drug interactions of warfarin, in sufficient awareness of patients about warfarin, and the high rate of comorbidities. In our study, INR was found to be 42% in the therapeutic range, and similar to this study, it is note worthy that the percentage of patients in the target INR was low.[8]

In a study conducted with a large patient group consisting of 29,717 AF and 19,113 VTE patients, it was observed that 43% of patients with AF and 36% of patients with VTE could reach the target INR. In this study, attention was drawn to the low level of reaching the target INR and it was stated that closer monitoring or innovative strategies were needed to optimize the results of oral anticoagulant treatment.[9]

In another study, the percentages of patients using warfarin for various indications reaching the effective INR were calculated and it was observed that 47.6% of the patients had an effective INR. In this study, it was emphasized that INR should be monitored more frequently, taking into account other medications used by the patients and their nutritional habits.[10]

In a study where the optimal INR range was taken as 2-3, the percentage of patients in the target INR range was determined as 50%. However, in this study, the therapeutic INR range was determined as 2-3 for all indications, and accordingly, the percentage of patients in different indications reaching the target INR was not determined. In addition, in this study, the INR range with the lowest risk of bleeding and thromboembolic events due to warfarin was determined as 1.8-2.4, a result different from the literature.[11]

In some studies conducted with patients with AF, the percentage of reaching the target INR was found to be 61-70%.[12,13] In our study, this was found to be 40%. The percentage of patients reaching the target in the above-mentioned studies is different from the literature, and it is thought that the reason why it is high is that the studies are prospective and are carried out in the form of clinical trials, resulting in beter and more effective follow-up.

In a meta-analysis, it was stated that the percentage of patients using warfarin reaching the target INR varied between 58% and 68%, depending on the median follow-up period. In this meta-analysis, warfarin was compared with new oral anticoagulants; New oral anticoagulants have been reported to have a favorable risk-benefit profile. New oral anticoagulants have been shown to have significant reductions in stroke, intracranial bleeding and mortality, but it has been emphasized that, similar to warfarin, they cause major bleeding and increase gastrointestinal bleeding. The advantage of this drug group is that it is more effective than warfarin, especially in stroke, and there is no need for INR monitoring, unlike warfarin. However, it has been stated that there is no clear superiority over warfarin in other indications, and much more experience and studies are needed for this group of drugs.[14]

In other studies in the literature, the percentage of reaching the target INR was found to be between 36.5-54%.[15-17] In our study, the percentage of reaching the target INR was found to be 42% in the total patient group, and when considered on the basis of indication, it was found to be 38.5% in patients with valve replacement, 40% in patients with AF, 54% in PTE patients and 70% in CVD patients. Although the results obtained from our study are generally compatible with the literature, the

percentage of reaching the target INR was found to be low, especially compared to studies conducted with prospective and clinical follow-up. The limitations of our study are that the number of patients diagnosed with PTE and CVD is small and that the factors affecting reaching the target INR, patient awareness and TTR cannot be determined due to the fact that our study is retrospective.

Conclusion

As a result, warfarin is a very frequently used drug today, and while the risk of thromboembolic events increases in patients with INR in the subtherapeutic range, serious bleeding is observed in cases with supratherapeutic INR. This causes serious morbidity and mortality. In our study, the percentage of patients reaching the target INR was found to be 42%. This rate is very low for such an important disease group, and in order to increase this rate, it is necessary to increase patient awareness, increase the frequency of follow-up of patients and develop more effective follow-up strategies.

Conflicts of Interest

There are no conflicts of interest in this work.

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CMJ,2024; 46(1): 45-51
DOI: 10.7197/cmj.1403570

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Surgical Outcomes and Recurrence Rates in Far Lateral Lumbar Disc Herniations: A Retrospective Analysis of 91 Cases

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Research Article

History

Received: 14/01/2024
Accepted: 22/03/2024

ABSTRACT

Objective: Far lateral lumbar disc herniations are distinct from intracanal herniations in clinical, radiological, and surgical aspects. This study aimed to assess surgical outcomes and recurrence risk factors for far lateral disc herniations treated with trans pars microsurgery.

Methods: Retrospective analysis included patients diagnosed with far lateral disc herniation who underwent Microscopic Transpars Discectomy at our university hospital between 2017 and 2022. Data encompassed demographics, pain characteristics, neurological status, radiological findings, surgical duration, pre/postoperative visual analog scale (VAS) and Oswestry Disability Index (ODI) scores, and late postoperative satisfaction rates.

Results: Of 91 patients (58.2% men, 41.8% women; mean age 57.42 ± 10.47 years), 76.92% had excellent outcomes, 16.48% good, and 6.5% fair; recurrence occurred in 5.5%. No significant differences were found between recurrent and non-recurrent cases in sex, age, herniation side, operation time, or levels ($p > 0.05$). Similarly, there were no significant differences in recurrent cases for pre/postoperative VAS ($p > 0.05$) or ODI scores ($p > 0.05$).

Conclusion: Microdiscectomy performed via transpars intervention is a safe and effective technique for the surgical treatment of far lateral disc herniation; age, sex, herniation level, herniation side, and VAS and ODI scores were not identified as recurrence risk factors.

Keywords: lumbar disc herniaton, fusion, microdiscectomy

Far Lateral Lomber Disk Herniasyonlarının Cerrahi Tedavi Sonuçları ve Nüks Oranları: 91 Vakanın Retrospektif Analizi

Araştırma Makalesi

Süreç

Geliş: 14/01/2024
Kabul: 22/03/2024

ÖZET

Amaç: Far lateral lomber disk herniasyonları klinik, radyolojik ve cerrahi yönlerden kanal içi herniasyonlardan farklılık gösterir. Bu çalışmanın amacı, trans pars mikrodiskektomi tekniği ile cerrahi tedavi uygulanan far lateral disk herniasyonlarının cerrahi sonuçlarını ve nüks risk faktörlerini değerlendirmektir.

Yöntem: 2017 ve 2022 yılları arasında üniversite hastanemizde far lateral disk herniasyonu tanısı ve trans pars mikrodiskektomi tekniği ile cerrahi tedavi uygulanan hastalar retrospektif olarak değerlendirilmek üzere çalışmaya dahil edildi. Değerlendirilen veriler; demografik ve ağrı özellikleri, nörolojik durum, radyolojik bulgular, cerrahi süre, ameliyat öncesi/sonrası vizüel analog skala (VAS) ve Oswestry Özürlülük İndeksi (ODI) skorları ve geç dönem postoperatif memnuniyet oranlarını kapsıyordu.

Bulgular: 91 hastanın (%58.2 erkek, %41.8 kadın; ortalama yaş 57.42 ± 10.47 yıl), %76.92'si mükemmel, %16.48'i iyi ve %6.5'i orta sonuçlar aldı; nüks %5.5 oranında gözlendi. Nüks eden ve etmeyen vakalar arasında cinsiyet, yaş, taraf, ameliyat süresi veya seviyeler açısından anlamlı farklılık bulunmadı ($p > 0.05$). Benzer şekilde, ameliyat öncesi/sonrası VAS ($p > 0.05$) veya ODI skorlarında ($p > 0.05$) nüks vakaları arasında anlamlı farklılık bulunmadı.

Sonuç: Transpars yaklaşım ile mikrodiskektomi, far lateral disk herniasyonun cerrahi tedavisinde güvenli ve etkili bir tekniktir; yaş, cinsiyet, herniasyon seviyesi, herniasyon tarafı ve VAS ile ODI skorları, nüks risk faktörleri olarak tanımlanmadı.

Anahtar Kelimeler: lomber disk herniasyonu, füzyon, mikrodiskektomi

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How to Cite: Doğu H. Surgical Outcomes and Recurrence Rates in Far Lateral Lumbar Disc Herniations: A Retrospective Analysis of 91 Cases, Cumhuriyet Medical Journal. 2024;46(1):45-51

Introduction

Far lateral lumbar disc herniation (FLLDH) is defined as a disc herniation located lateral to the medial wall of the pedicle. FLLDH can be foraminal, intraforaminal, far lateral, and extreme far lateral depending on their localization and are less common compared to disc herniations within the spinal canal. FLLDH constitutes 7%–12% of all herniated discs.[1] FLLDH differs from disc herniations located in the spinal canal by certain characteristics. FLLDHs are more prevalent in the elderly and compress the descending root from the upper segment and have the potential to cause more severe pain because of the likelihood of compressing the ganglion.

The clinical presentation of far lateral lumbar disc herniations and the surgical techniques in use are different. Despite the fact that more invasive techniques, including facetectomy,[2] were initially used in surgery, there is now a trend toward more minimal techniques because of unsatisfactory results and instability of the former techniques. Today, the most frequently used techniques include microscopic trans-pars discectomy, minimally invasive surgery, tubular discectomy, micro-endoscopic discectomy, and full endoscopic discectomy.

There are several previous studies in the relevant literature on surgical techniques and short- and long-term outcomes of FLLDHs.[1, 3, 4, 5, 6] However, there are only a limited number of studies with a focus on recurrence and the surgical treatment thereof.[7] The present study reports the results of far lateral disc herniations operated with trans pars microsurgery, as well as the risk factors, surgery, and outcomes of recurrences.

Materials and Methods

This present retrospectively assessed the patients diagnosed with FLLDH, who underwent surgical treatment with microscopic trans-pars discectomy at our University Hospital between 2017 and 2022.

Ethics committee approval of our university hospital (approval number: E-22686390-050.99-24887) was obtained. Age, sex, pain characteristics, neurological status, radiological features, duration of surgery, preoperative and postoperative visual analog scale (VAS) scores, and follow-up duration were recorded for all the patients. Postoperative patient satisfaction was assessed based on the MacNab classification as excellent (no pain), good (mild pain), fair (moderate pain), and poor (unchanged or more severe pain). The Oswestry Disability Index (ODI) was used to assess the patients' physical capacity in relation to limitation in activities in daily life and returning to work in the pre- and post-operative period.[8] Radicular pain lasting 4–6 weeks, progressive neurologic deficit, and severe pain not adequately responsive to analgesics were determined as indications for surgery. All patients underwent magnetic resonance imaging (MRI) and FLLDH compressing the upper root were included in the study. Patients with herniation at another level or in the same segment or with stenosis and instability were excluded from the study.

Surgical technique

All the patients were operated in prone position under either spinal or general anesthesia. Upon level determination by fluoroscopy, a 2.5–3 cm incision was made in the midline, fascia was incised, and muscles were dissected. The parts of the upper and lower facet facing the pars and the pars itself were exposed. During the microscopic-assisted procedure, the lamina was advanced using a drill from the lateral aspect of the pars and a 1–1.5 cm laminotomy was performed with a Kerrison Rongeur. The transverse ligament was removed and the upper root was exposed. Based on MRI results, the disc was reached by proceeding according to the localization of the disc compressing the root. The disc fragments were removed and the discectomy procedure was completed. Patients were mobilized after 6 hours. The patients were discharged 1 day later.

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) software, Version 26, was used for the statistical analysis in assessment of the study results Accordingly, quantitative variables were represented by mean, standard deviation, median, min and max values, and qualitative variables were represented by descriptive statistical methods, including frequency and percentage. Shapiro Wilks test and Box Plot graphs were used to test the normal distribution hypothesis of the study data.

Mann–Whitney U test was used in the two-group analyses of variables without normal distribution and Wilcoxon Signed Rank test was used for the purpose of intragroup analyses.

The Fisher's Exact test and Fisher Freeman Halton test were used to compare qualitative data.

Results were evaluated at 95% confidence interval and a p value of <0.05 was considered statistically significant.

Results

The study was conducted at our University Hospital between 2017 and 2022 with a total of 91 patients, 58.2% (n = 53) men and 41.8% (n = 34) women. The patients' ages ranged between 39 and 86 years with a mean age of 57.42 ± 10.47 (Table 1).

56% (n = 51) of the patients had herniation on the right side and 44% (n = 40) on the left side upon analysis. The duration of anesthesia operation varied between 1.05 and 2.33 hours in the patients; where the mean duration was 1.48 ± 0.37 hours. Recurrence was observed in 5.5% (5) of the patients. As regards the levels of hernia in the patients, 2.2% (n = 2) were at L1-2, 7.7% (n = 7) at L2-3, 22% (n = 20) at L3-4, 38.5% (n = 35) at L4-5, and 29.7% (n = 27) at L5-S1.

The mean preoperative VAS score of the patients included in the study was 7.26 ± 0.96, where the mean postoperative VAS score was 1.99 ± 0.77. The mean preoperative ODI score of the patients was 76.64 ± 12.5, where the mean postoperative ODI score was 8.76 ± 5.01.

All patients had radicular pain. Thirty patients (32.96%) had motor deficits. 55 cases (60.43%) presented with sensory changes. The duration of preoperative

complaints ranged from 3 days to 2.5 months. Of the 30 patients with motor deficits, 23 (76.66%) recovered completely, 5 (16.66%) recovered partially, and 2 (6.66%) showed no improvement. Complaints decreased in 32 (58.18%) out of 55 cases with sensory changes. The outcome was excellent in 76.92% (70), good in 16.48% (15), and fair in 6.5% (6) of the patients.

Motor deficit increased in 3 (3.29%) patients post-operatively. Improvement seen within weeks upon introduction of physical therapy. Neuropathic pain persisted postoperatively in 7 patients, who were administered gabapentin treatment for 4 weeks to 6 months. All the patients reported no neuropathic pain or minor symptoms thereof at the end of the above periods. Superficial infection occurred in 2 patients. They recovered upon 10-day antibiotic treatment and wound care.

Table 1: Distribution of Descriptive Characteristics

	n (%)	
Sex		
Men	**53 (58.2)**	
Women	**38 (41.8)**	
Age		
Mean ± SD		**57.42 ± 10.47**
Median (Min-Max)		**57 (39-86)**
Side		
Right	**51 (56.0)**	
Left	**40 (44.0)**	
Duration of op. anesthesia (hours)		
Mean ± SD		**1.48 ± 0.37**
Median (Min-Max)		**1.5 (1–2.33)**
Recurrence		
No	**86 (94.5)**	
Yes	**5 (5.5)**	
Level		
L1–2	**2 (2.2)**	
L2–3	**7 (7.7)**	
L3–4	**20 (22.0)**	
L4–5	**35 (38.5)**	
L5–S1	**27 (29.7)**	
Preop VAS		
Mean ± Sd		**7.26 ± 0.96**
Median (Min-Max)		**7 (6–9)**
Postop VAS		
Mean ± Sd		**1.99 ± 0.77**
Median (Min-Max)		**2 (1–3)**
Preop ODI		
Mean ± Sd		**76.64 ± 12.5**
Median (Min-Max)		**80 (45–100)**
Postop ODI		
Mean ± Sd		**8.76 ± 5.01**
Median (Min-Max)		**9 (1–20)**

Post-operative recurrence occurred in 5 patients between Day 20 and 96. The same surgical treatment technique (trans-pars approach and microsurgery) was used in 2 of these patients, and in the other 3 patients, posterior short segment pedicle screw and posterolateral fusion were additionally applied. (Figure-1) One patient, who underwent microsurgical revision had recurrence and received fusion surgery during the 3rd operation.

There was no statistically significant difference in recurrent cases based on sex, age, side, operation time, and disc herniation levels ($p > 0.05$) (Table 2). There was also no statistically significant difference in recurrent cases by preoperative and postoperative VAS scores ($p > 0.05$) (Table 3), and by preoperative and postoperative ODI scores ($p > 0.05$) (Table 4).

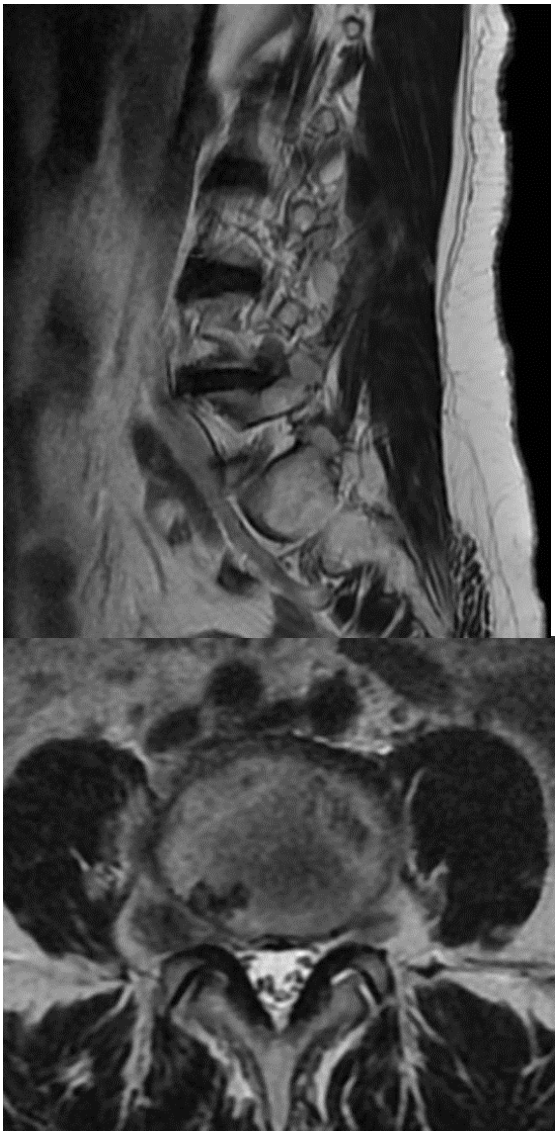

Fig 1 a.b. Preoperative sagittal and axial magnetic resonance images of a 53-year-old female patient with right L4-5 far lateral disc herniation.

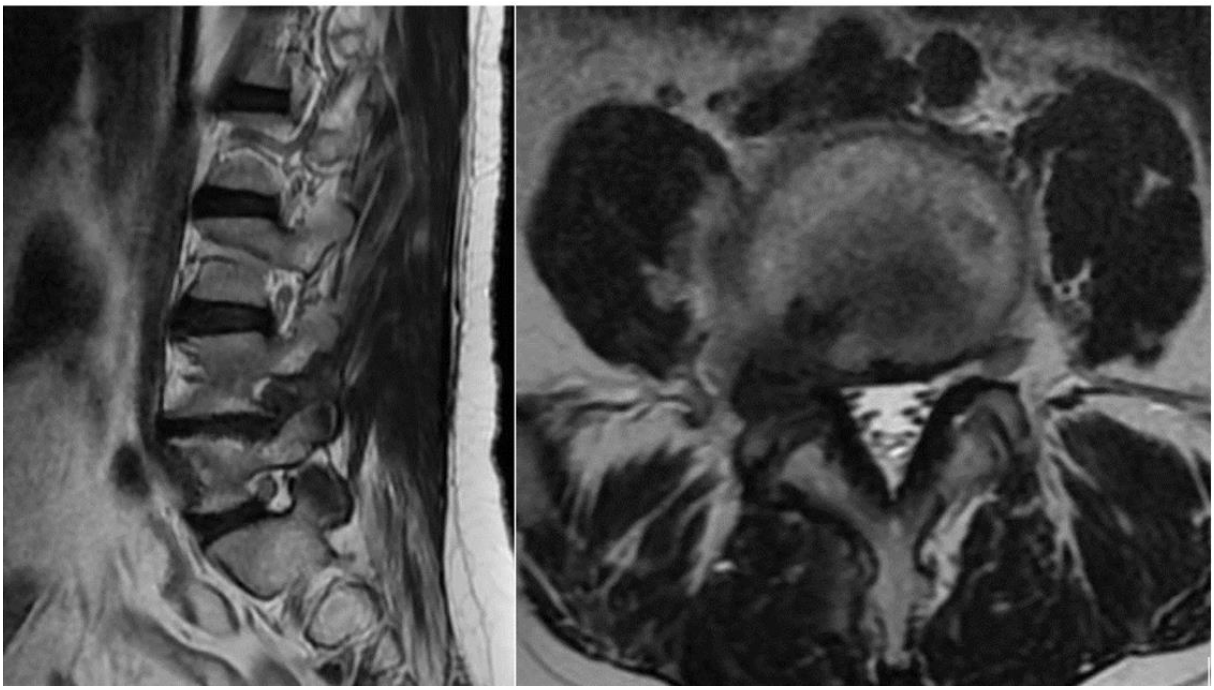

Fig 1 c.d. Lumbar magnetic resonance was performed because the patient had right radiculopathy 11 months after the surgery. Recurrent far lateral lumbar disc herniation was observed on magnetic resonance images

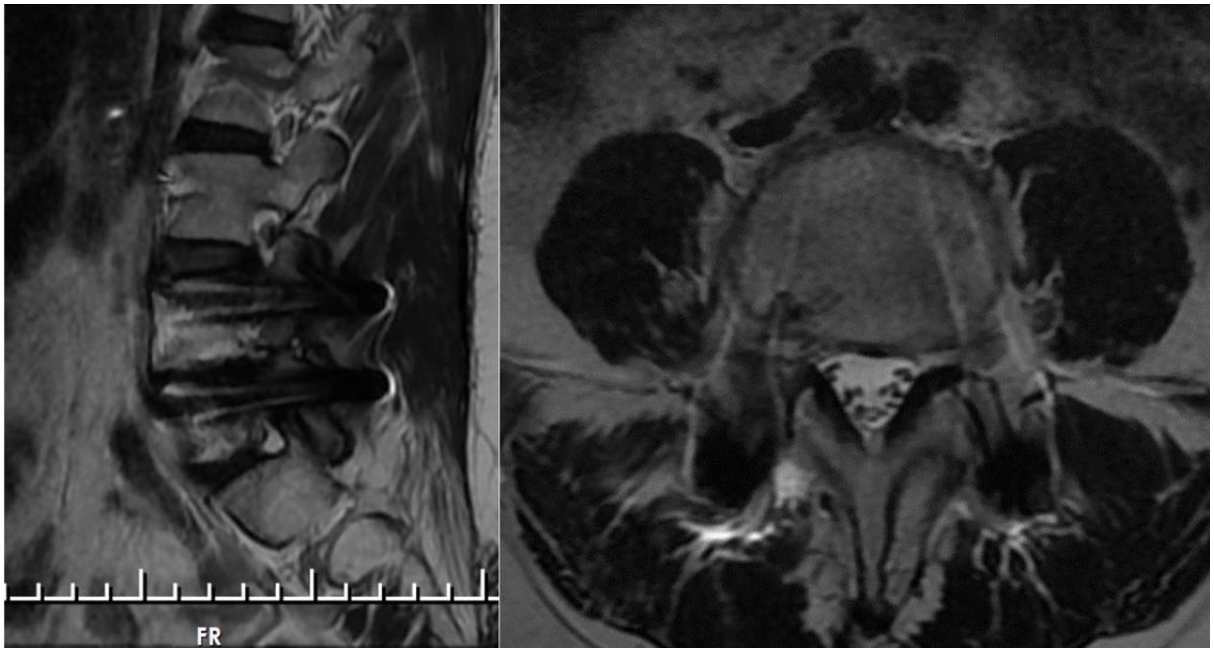

Fig 1 e.f. The patient underwent revision surgery with trans-pars microdiscectomy and fixation surgery with short segment pedicle screw technique. Postoperative sagittal and axial magnetic resonance images.

Table 2: A Comparison of descriptive characteristics between recurrent and nonrecurrent cases.

	Recurrence		p
	No (n=86)	Yes (n=5)	
Sex			
Men	50 (58.1)	3 (60.0)	1.000[a]
Women	36 (41.9)	2(40.0)	
Age			
Mean ± SD	57.26±10.65	60.2±7.05	0.418[b]
Median (Min-Max)	56.5 (39–86)	62 (53–69)	
Side			
Right	49 (57.0)	2 (40.0)	0.651[a]
Left	37 (43.0)	3 (60.0)	
Duration of operation (hours)	1.47±0.37	1.62±0.46	
Mean ± SD	1.47±0.37	1.62±0.46	0.385[b]
Median (Min-Max)	1.5 (1–2.3)	1.8 (1–2)	
Level			
L1–2	2 (2,3)	0 (0,0)	
L2–3	7 (8,1)	0 (0,0)	
L3–4	18 (20,9)	2 (40.0)	0.832[c]
L4–5	33 (38,4)	2 (40.0)	
L5–S1	26 (30,2)	1 (20,0)	

a.Fisher Exact Test
b.Mann–Whitney U Test
c.Fisher Freeman Halton Test

Table 3. A comparison of VAS scores between recurrent and nonrecurrent cases

		Recurrence		p
VAS		No (n=86)	Yes (n=5)	
Preop	Mean±SD	7.27±0.98	7.20±0.84	0.964[b]
	Median (Min-Max)	7 (6–9)	7 (6–8)	
Postop	Mean±SD	2.0±0.77	1.80±0.84	0.571[b]
	Median (Min-Max)	2 (1–3)	2 (1–3)	
	p	0.001[d,**]	0.038[d,*]	
Difference Δ	Mean±SD	−5.27±1.25	−5.40±0.55	0.712[b]

b.Mann–Whitney U Test; d.Wilcoxon Signed Rank Test
**p < 0.01 *p < 0.05

Table 4: A comparison of ODI scores between recurrent and nonrecurrent cases

		Recurrence		p
ODI		No (n=86)	Yes (n=5)	
Preop	Mean±SD	76,84±12,53	73,20±12,70	0,488[b]
	Median (Min-Max)	80 (45–100)	75 (56-85)	
Postop	Mean±SD	8,62±5,02	11,20±4,66	0.270[b]
	Median (Min-Max)	9 (1–20)	10 (6-17)	
	p	0.001[d,**]	0.043[d,*]	
Difference Δ	Mean±SD	-68,2±13,32	-62,0±12,98	0.299[b]

b.Mann–Whitney U Test; d.Wilcoxon Signed Rank Test
**p < 0.01 *p < 0.05

Discussion

The surgical treatment of far lateral lumbar disc herniations should aim to relieve pain, remove neurological compression, and maintain stability. Neurologic deficits, neuropathic pain, limitation of daily activity, and recurrences are considered among the most important factors affecting the outcomes of surgical treatment.[9] Therefore, there is a trend associated with the increased use of minimally invasive techniques in the surgical treatment of far lateral lumbar disc herniations. Furthermore, there are different approaches in use, including the trans-pars approach, paravertebral muscle separation approach, and endoscopic approach.[4,5,10] There is no consensus with regard to the surgical technique of choice. Each approach is associated with particular advantages and disadvantages.

The risk factors for recurrent herniation upon surgical treatment of far lateral disc herniations, re-operation techniques and especially the outcomes of re-operation have not yet been sufficiently discussed in the relevant literature. There are only a limited number of suggestions on whether the factors that affect the occurrence of intra-canal herniations are also active in the far laterals. Chang SB et al. reported 9 recurrent cases out of 184 patients, who underwent micro-decompression by lateral intermuscular access.[11] They reported that double herniations (both intra-canal and far lateral coexistence) were more likely to have a poor outcome where factors, including age and sex did not affect the poor outcome. Recently, Monticelli et al. reported 6 recurrent cases and performed surgery in 5 of them in a series of 135 cases, which underwent surgical treatment via trans-pars.[7] Consistently, they reported that the variables (age/sex/body mass index (BMI)/treated level) did not affect the outcome.

Park et al. reported 209 (11%) recurrent cases in patients who underwent transforaminal endoscopic lumbar disc decompression in a series of 1900 cases and suggested that small herniations recurred more frequently.[12] They further reported that recurrences usually occurred within the first month and even 12.9% occurred during the first 24 hours of surgery. They reported that age, sex, diabetes mellitus (DM), hypertension (HTN), smoking status, BMI, nature of disc herniation, modic changes, migration grade, height of herniated disc, and spondylolisthesis had no effect on recurrence. Similarly, in the present study, age, sex, herniation segment level, side of herniation, and duration of surgery were not risk factors for recurrence.

It is considered that surgical treatment of recurrent far lateral lumbar herniation is challenging. For intra-canal recurrent herniations, it may be possible to dissect the dura and root relatively mesial to the facet when a fibrotic area is encountered at the laminotomy site. Otherwise, as we and certain other authors suggest, it is possible to fix the root caudally over the foramen, dissect it and exclude it. The surgical treatment of far lateral disc herniations differs on the grounds that there are no similar anatomical

structures in the surgical field. We found advanced fibrosis between the root and the inferior facet in all cases of recurrent far lateral herniations. As have been reported by certain authors, dissecting this fibrotic tissue can prove to be a highly challenging process.[1] Therefore, it was possible to access the disc fragments upon dissection from the upper edge of the inferior facet, which was safer.

Previous studies in the relevant literature included different surgical techniques of choice for the revision surgery of far lateral lumbar disc herniations. Chang SB et al. reported 9 recurrent cases, who received revision surgery thereafter.[11] Revision discectomy was the surgical technique of choice in 1 case, total disc replacement in 1 case and fusion in 7 cases. Recently Alhashash M et al. used the Extra-laminar microscopic-assisted percutaneous nucleotomy technique in a series of 50 cases.[13] There were 2 recurrent cases. These two cases were reoperated using the same technique. Sasani et al. performed percutaneous discectomy in 66 cases and reported three recurrent cases.[14] They opted for microsurgery for the reoperation of recurrent cases. In their series of 22 cases, Thomas Lübbers et al. removed only L 5-S 1s using the percutaneous endoscopic surgery technique. One patient with recurrent hernia was re-operated by open surgery.[9]

Another issue of the ongoing debate is whether only extruded or free fragments should be removed in far lateral discs or the disc space should be evacuated. Chan Hong Park et al. reported that inaccessible fragments and inadequate decompression during surgery were associated with early recurrences.[12] Therefore, they suggested that it was critical to remove both extruded and accessible basal fragments. In the cases included in the present study, if the laminotomy area provided access to the disc space, if the post longitudinal ligament was ruptured in that area and a fragment was observed in the distance where there was a risk of rupture, the disc space was entered and the disc space was evacuated. Only the compressing disk fragments were removed, where the above conditions were not met.

Upon a review of the relevant literature, the recurrence time for intracanal lumbar discs varies between 1 and 5 years, where this period is slightly shorter in recurrent far lateral disc herniations (1 day to 32 months).[3,11, 12, 13] In the series included in this study, postoperative recurrence occurred in 5 patients between the 20th and 96th days. It was reported that the cause of early recurrences was associated with insufficient fragment removal or inadequate decompression.[12]

In the series included in the previous studies, different techniques were used for revision surgeries of recurrent cases. These techniques were the same as the first surgical technique, that is, endoscopic, microsurgery, etc., or fusion surgery was the technique of choice. It was not clear which technique should be applied due to the limited research on this subject. There were 5 recurrent cases in the series included in the present study. In 2 cases, microscopic trans-pars technique was used for revision surgery, where pedicle screw fixation and posterolateral fusion surgery was opted for the remaining 3 cases. One of the cases, who underwent microscopic trans-pars procedure, developed recurrence and pedicle screw fixation and posterolateral fusion were performed in the same way subsequently.

Limitation

Certain parameters, including intervertebral disc height, facet angle, herniation size, amount of fragments removed, BMI, DM, and HTN were not included in this study. These need to be taken into consideration as they may have an effect on recurrence. The present study was designed as retrospective research, future prospective studies may contribute to a better understanding of the subject. It is necessary to perform a multi-center study with an adequate sample size, in order to compare the surgical techniques applied in recurrent far lateral lumbar disc herniations. In our cases, fusion approach was the most frequently used technique for the surgical treatment of recurrences. The outcomes of revision surgery without fusion procedure should be monitored.

Conclusion

The microsurgical trans-pars procedure is a safe and effective option for the surgical treatment of far lateral lumbar disc herniations. Surgical removal of far lateral disc prolapse can be performed at all lumbar levels with minimal bone resection without the risk of instability and without restrictions. Age, sex, level, side of hernia development, and VAS and ODI scores were not risk factors for recurrence.

Conflict of Interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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CMJ,2024; 46(1): 52-56
DOI: 10.7197/cmj.1324648

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Diagnostic Contribution of Diffusion-Weighted Imaging in Liver Hemangiomas

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Research Article

History

Received: 17/07/2023
Accepted: 07/03/2024

ABSTRACT

Objective: The purpose of this study is to evaluate the contribution of diffusion weighted (DWI) MRI and measured appearent diffusion coefficient (ADC) values in hepatic hemanjiomas.
Methods: The study population consisted of 70 patients with liver hemangiomas. DWI examination with a b value of 800 s/mm2 was carried out for all patients. After DWI examination, an ADC map was created and ADC values were measured for 70 liver masses and normal liver tissue (control group). ADC measurement of 70 normal liver parenchyma and, mean ADC values of 80 hemangiomas are performed.
Results: Eighty hemangiomas of 70 patients composed by 50 women and 20 men are evaluated in our study. Age of the patients who included to study are between 26 and 73 and the mean age was calculated 49.61 ± 10.96. Hemangiomas are shown most highly at segment 7 (%28.8) and segment 6 (%21.3), and least at segment 5 (%5). While the mean ADC measurement of normal livers of patientes are included to study was 1.06 ± 0.11 x 10-3 mm2 /s, the mean ADC value of hemangiomas was measured 1.70 ± 0.29 x 10-3 mm2/s.
Conclusion: DWI, and measurements of ADC values obtained from process are useful for the diagnosis of hemangioma. We think that DWI should be routinely added to convantional MR sequences.

Keywords: Liver, Diffusion weighted imaging, Magnetic resonance imaging, Apparent diffusion coefficient, Hemangioma

Karaciğer Hemanjiyomlarında Difüzyon Ağırlıklı Görüntülemenin Tanısal Katkısı

Araştırma Makalesi

Süreç

Geliş: 17/07/2023
Kabul: 07/03/2024

ÖZET

Amaç: Bu çalışmanın amacı, hepatik hemanjiomlarda difüzyon ağırlıklı (DAG) MR ve ölçülen görünen difüzyon katsayısı (GDK) değerlerinin katkısını değerlendirmektir.
Yöntem: Çalışma grubunu karaciğer hemanjiomlu 70 hasta oluşturdu. Tüm hastalara b değeri 800 s/mm2 olan DAG incelemesi yapıldı. DAG incelemesi sonrasında GDK haritası oluşturuldu ve 70 karaciğer kitlesi ve normal karaciğer dokusu (kontrol grubu) için GDK değerleri ölçüldü. 70 normal karaciğer parankiminin GDK ölçümü ve 80 hemanjiomun ortalama GDK değerleri yapıldı.
Bulgular: Çalışmamızda 50'si kadın, 20'si erkek olmak üzere 70 hastanın 80 hemanjiyomu değerlendirildi. Çalışmaya alınan hastaların yaşları 26 ile 73 arasında olup yaş ortalaması 49,61±10,96 olarak hesaplandı. Hemanjiomlar en fazla segment 7 (%28,8) ve segment 6'da (%21,3), en az ise segment 5'te (%5) görülmektedir. Çalışmaya dahil edilen hastaların normal karaciğerlerinin ortalama GDK ölçümü 1,06 ± 0,11 x 10-3 mm2/sn iken, hemanjiomların ortalama GDK değeri 1,70 ± 0,29 x 10-3 mm2/sn olarak ölçüldü.
Sonuç: DAG ve işlem sonrası elde edilen GDK değerlerinin ölçümü hemanjiyom tanısı için faydalıdır. Geleneksel MR sekanslarına DAG'nin rutin olarak eklenmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: Karaciğer, Difüzyon ağırlıklı görüntüleme, Manyetik rezonans görüntüleme, Görünür difüzyon katsayısı, Hemanjiom

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How to Cite: Akın Rİ, Atalar HM, Başpınar N, Şeker B, Yılmaz G. Diagnostic contribution of diffusion-weighted imaging in liver hemangiomas, Cumhuriyet Medical Journal. 2024;46(1):52-56

Introduction

Hemangioma is the most common benign tumor of the liver.[1]Due to the asymptomatic nature, these are usually observed incidentally while routine imaging.[2]Hemangiomas represent a minor rate of complications and uncomplicated lesions do not require surgical resection. Therefore, it is important that hemangiomas are diagnosed by imaging.[1]

Magnetic resonance imaging (MRI) is the best imaging modality for diagnosing hemangiomas.[3] Diffusion-weighted imaging (DWI) offers better results for detecting and characterizing liver lesions than T2-weighted imaging. It can also provide additional contributions to contrast-enhanced sequences.[4] DWI is a technique that is measures the Brownian motion alterations of water molecules in the tissue. The apparent diffusion coefficient (ADC) is calculated from DW images.[5,6] Some studies in the current literature showed that ADC values can be used in the differential diagnosis of hepatic pathologies. [7, 8, 9, 10]

The aim of this study is to reveal the contribution of DWI and measure the ADC values of hepatic hemangiomas.

Materials and methods

Patient Group

The Institutional Review Board approved this retrospective study (Date: 16.04.2014 - No: 2014-04/13). PACS (Picture archiving and communication system) of our University, Department of Radiology was reviewed from August 2012 and March 2014, and 70 patients of over 18 age adults who were already diagnosed with hemangioma by computed tomography (CT), or ultrasonography (US), or directly imaged by MRI with suspicion of hemangioma. Patients with pathology other than liver hemangioma (hepatosteatosis, biliary obstruction, cirrhosis, etc.) were excluded from the study. Patients with poor general conditions, respiratory problems, and cases with a prosthesis, implants, or cardiac pacemakers were not included in the study. Lesions smaller than 8 millimeters were excluded, because the ADC value measurement would not be optimal. The diagnosis of the hemangioma was performed according to the previous characteristic US, CT, and dynamic liver MRI results. The atypical-looking hemangiomas were not included in the study.

MR Imaging Protocol

A 1.5 Tesla superconducting MR scanner (Magnetom Aera, Siemens Healthcare, Erlangen, Germany) was performed without sedation in a supine position for imaging. Fat-suppressed TSE T2-weighted (T2W), TSE heavy T2W, gradient echo in-phase and opposite-phase T1-weighted (T1W), contrast-enhanced dynamic T1W images were obtained in all patients routinely.

DWI examination was performed before contrast agent administration. DWI studies were independently reviewed by two experienced radiologists for all cases. Diffusion-weighted sequences were performed in the axial plane. Two different b values (b = 0 s/mm2 and b = 800 s/mm2) were used in diffusion-weighted imaging. To obtain ADC values, multiple Regions of Interest (ROI)s were marked within the hemangiomas and in normal-appearing liver parenchyma not involved by the hemangioma using the same ROIs for signal intensity calculation. The measured ROI diameter was set at approximately 1 cm. Three consequent measurements were made for each lesion, and normal liver parenchyma in consecutive sections, and the mean values were calculated. The mean ADC value was used for analysis.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) 22.0 (IBM Corp., Armonk, NY, USA). When parametric test assumptions were fulfilled the significance test of the difference between the two means was used, and when the parametric test assumptions were not fulfilled, Man-Whitney U test, Chi-square test, and correlation analysis were applied. A value of $p<0.05$ is considered statistically significant.

Results

Eighty hemangiomas of 70 patients (50 female and 20 male) were evaluated in our study. The ages of the patients included in the study were between 26 and 73 and the mean age was 49.61 ± 10.96. Hemangiomas are shown most highly at segment 7 (%28.8) and segment 6 (%21.3), and least at segment 5 (%5). The mean ADC values of healthy liver parenchyma represented statistically significant difference for both genders (p<0,05). While the mean ADC measurement of healthy livers of female patients was 1.04 ± 0.11 x 10-3 mm2/s, the mean ADC value of male patients was measured 1.12 ± 0.13 x 10-3 mm2/s. When ADC values of hemangiomas were compared with healthy liver ADC values regarding age groups, the difference was not statistically significant (p> 0.05)

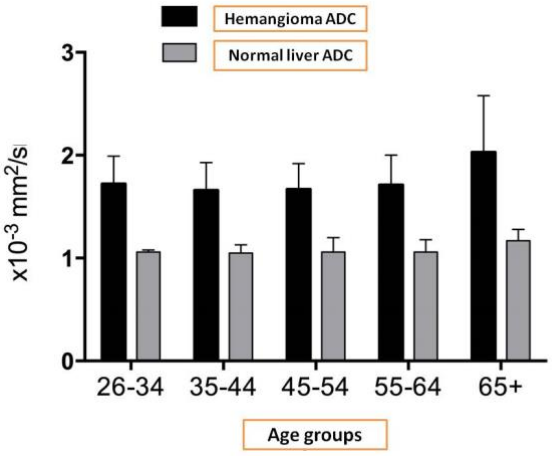

Figure 1. Comparison of hemangioma and normal liver ADC values by age groups.

No significant difference was observed when the two genders were compared (p>0.05). The mean ADC measurements of hemangiomas were 1.72 ± 0.30 x 10-3 mm2/s in females and 1.76 ± 0.32 x 10-3 mm2/s in males. Figures 2 and 3 show the MR images of the cases. In this

current study, the mean ADC values of hemangiomas were not significantly different between gender groups. In addition, the mean ADC values of healthy liver parenchyma showed no statistically significant. difference between gender groups.

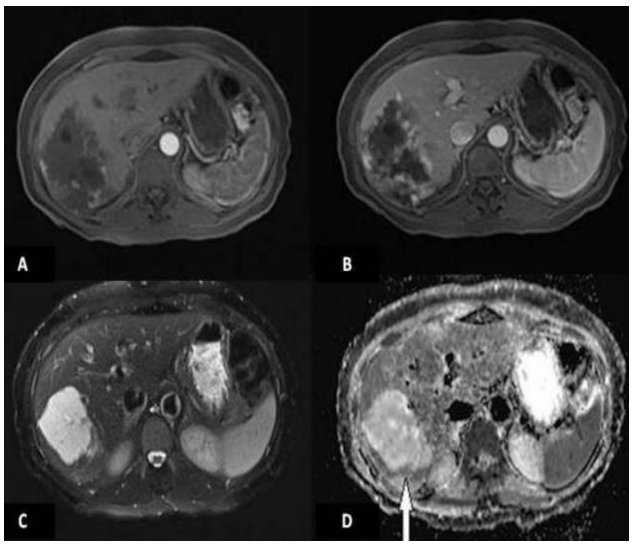

Figure 2. The female patient in 49-year-old. In the dynamic liver MRI of the patient, it is seen that the hemangioma shows peripheral nodular enhancement and progresses towards the center (a, b, c). The giant hemangioma observed in segment 6 in the fat-suppressed T2W image (d) is significantly hyperintense compared to the liver parenchyma. In ADC mapping (e), the mean ADC value of the lesion (arrow) was 1.15x10-3 mm2/s, while the average ADC values obtained from the healthy liver were measured as 1.02x10-3 mm2/s.

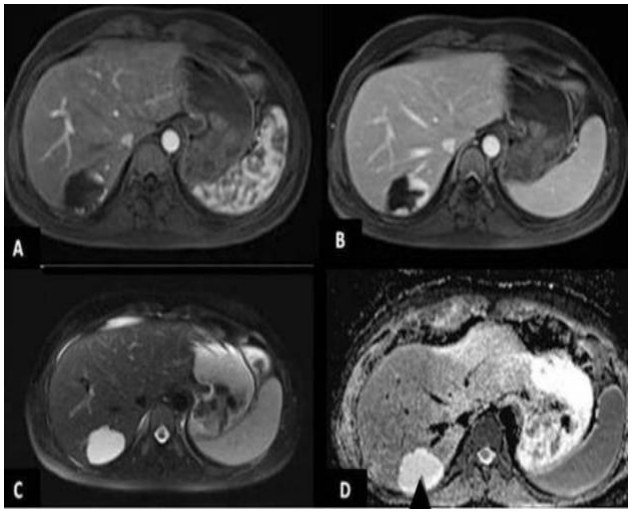

Figure 3. The male patient in 38-year-old. In the dynamic liver MRI of the patient, it is seen that the hemangioma shows peripheral nodular enhancement and progresses towards the center (a, b). The giant hemangioma observed in segment 6 in the fat-suppressed T2W image (c) is significantly hyperintense compared to the liver parenchyma. In ADC mapping (d), the mean ADC value of the lesion (arrow) was 1.85x10-3 mm2/s, while the average ADC values obtained from the healthy liver were measured as 1.07x10-3 mm2/s.

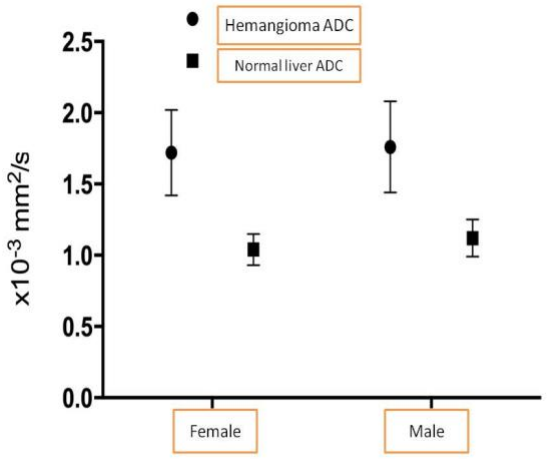

Figure 4. Comparison of hemangioma and normal liver ADC values by gender.

When comparing the mean ADC value of both hemangiomas and healthy liver parenchyma; the mean ADC value of the hemangiomas was significantly higher than the mean ADC value of healthy liver parenchyma (p<0,05). While the mean ADC value of healthy livers was measured 1.06 ± 0.11 x 10-3 mm2/s, the mean ADC value of hemangiomas was measured 1.70 ± 0.29x10-3 mm2/s.

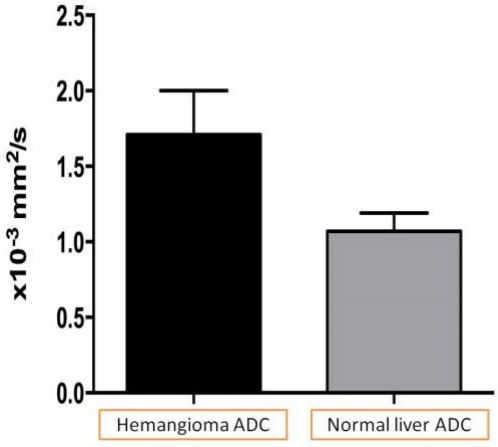

Figure 5. The distribution of the study groups according to the average ADC values with the box-plot chart.

Discussion

In some cases, it can be difficult to distinguish malignant liver tumors from hemangiomas in routine MRI. Because some hemangiomas may show atypical patterns on postcontrast MRI series, or decreased signal intensity on T2W images.[11, 12]

DWI has been shown to help identify focal liver lesions.[13,14] Furthermore, some previous studies at the literature have shown that ADC measurements are significantly different in benign and malignant liver lesions.[9,15-19] Hemangiomas contain a wider extracellular distance than normal tissue. Therefore, hemangiomas have

with free diffusion and elevated apparent diffusion coefficient (ADC) values.[20]

The sensitivity of the image is determined by chancing b values in DWI. High b values should be selected to best evaluate liver masses and common liver diseases in abdominal imaging.[4, 21, 22] However, because of the healthy liver parenchyma has short T2 relaxation time, the b value should not be higher than 1000 s/mm2.[4] In our study, ADC measurements were obtained from diffusion imaging with b-800 s/mm2 value.

In recent literature, there are many studies comparing normal liver parenchyma with hemangioma. Moteki et al.[8] reported that the mean ADC value of healthy liver parenchyma was 1.16 x 10-3 mm2/s, the mean ADC value of hemangiomas was 2.23 x 10-3 mm2/s. Hemangiomas had significantly higher ADC values than healthy liver parenchyma (p <0.05). Tokgoz et al.[17] reported that the mean ADC value of healthy liver parenchyma was 1.61 x 10-3 mm2/s, the mean ADC value of hemangiomas was 2.70 x 10-3 mm2/s. Hemangiomas had significantly higher ADC values than healthy liver parenchyma (p <0.001). Taouli et al. reported that the mean ADC value of healthy liver parenchyma was 1.83 x 10-3 mm2/s, the mean ADC value of hemangiomas was 2.95 x 10-3 mm2/s. Hemangiomas had significantly higher ADC values than healthy liver parenchyma (p <0.01).[23] Namimoto et al. [24] reported that the mean ADC value of healthy liver parenchyma was 0.69 x 10-3 mm2/s, the mean ADC value of hemangiomas was 1.95 x 10-3 mm2/s. Hemangiomas had significantly higher ADC values than healthy liver parenchyma (p <0.01). Bozgeyik et al.[25] reported that lower ADC values were obtained in higher b values (b=1000) in normal liver tissue and hemangiomas. The mean ADC value of healthy liver parenchyma was 1.14x10-3 mm2/s, the mean ADC value of hemangiomas was 1.60 x 10-3 mm2/s. Hemangiomas had significantly higher ADC values than healthy liver parenchyma (p <0.01). These results were consistent with our study. In our study, the Mean ADC value of healthy liver parenchyma was significantly lower than hemangiomas. The mean ADC values of healthy liver parenchyma was 1.06 ± 0.11 x 10-3 mm2/s and hemangiomas were 1.70 ± 0.29 x 10-3 mm2/s. Significant statistical difference in ADC values between hemangiomas and healthy liver parenchyma was demonstrated. (P <0.05). Parikh et al.[26] reported that the mean ADC value of hemangiomas 2.04 x 10-3 mm2/s. Similarly, Kim et al.[27] reported the mean ADC value of hemangiomas was 2.04 x 10-3 mm2/s.

The ADC value of hemangiomas is higher than solid malign lesions but are lower than cysts. This is probably related to the vascular structure of hemangiomas that are more viscous than cystic fluid. Furthermore, the ADC value of malign lesions are lower than benign lesions which is probably due to their tumoral cellular content.[23, 24, 28]

In our study, there was no significant difference between lesion size and ADC values. Lesion size did not alter ADC values significantly. Similarly to our results, Bozgeyik et al.[25] and Goshima et al. [29] found no statistical correlation between lesion size and ADC values. In addition to in our study, the mean ADC values of hemangiomas were not significantly different between age groups.

There are few limitations in our study. Firstly, our study population was relatively small. Second limitation was related with the examination technique. DDWI was done with sequences sensitive to physiological movements such as respiratory, cardiac, and intestinal peristalsis. Therefore, the image quality is affected. Thirdly, our study was performed on a 1.5 T MR device. Another limitation, a separate ADC value was not calculated for each b value. It is also a limitation that ADC values are not compared with malignant lesions.

Conclusion

DWI, and measurement of ADC values may be useful both in the differential diagnosis of benign and malignant liver lesions and in the diagnosis and differentiation of hemangiomas. Hemangiomas have higher ADC values than malignant lesions and healthy liver parenchyma, but they have lower ADC values than cysts. DWI and ADC values may be helpful in primary and differential diagnosis of hemangiomas. DWI also has the advantage that it does not require contrast material and is a fast sequence.

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CMJ. 2024;46(1):57-65
DOI: 10.7197/cmj.1431762

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Determination of Serum Interleukin-36 Alpha, Beta, Gamma and Interleukin-17 Levels in Patients with Multiple Myeloma

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Research Article

History

Received: 06/02/2024
Accepted: 23/03/2024

ABSTRACT

Objective: Multiple myeloma (MM) is a hematologic malignancy characterized by bone marrow infiltration of clonal plasma cells. Today, there is no treatment for obtaining a complete cycle for MM. IL-36 is a cytokine composed of three agonists named alpha, beta, and gamma. Its increase in inflammation has been proven in the literature. It is also reported that IL-17 plays a role in some rheumatologic and malignant diseases together with inflammation.

Methods: The aim of the study is to figure out the roles, if any, of IL-36 and IL-17 in the pathogenesis of MM depending on their known physiology and to contribute to the literature to find new treatment options.

33 newly diagnosed MM patients who had never received any treatment and 33 healthy volunteers were included in the study. Basic laboratory parameters and interleukin levels in myeloma patient group and healthy group were included in the study.

Results: In the study, it was found that IL-36 alpha, beta, gamma, and IL-17 levels were statistically significantly lower in the disease group when compared to the healthy group. A negative correlation was found between IL-17 measurement and beta-2 microglobulin. Therefore, it was thought that IL-17 may be a marker to predict prognosis.

Conclusion: In conclusion, we think that IL-36 and IL-17 may play a role in the etiopathogenesis of MM and IL-36 alpha and IL-17 may be associated with prognosis. However, there is a need for more comprehensive studies.

Keywords: Multiple myeloma, Interleukin 36, Interleukin 17

Multipl Myelomali Hastalarda Serum İnterlökin-36 Alfa, Beta, Gama; İnterlökin-17 Düzeyinin Belirlenmesi

Araştırma Makalesi

Süreç

Geliş: 06/02/2024
Kabul: 23/03/2024

ÖZET

Amaç: Multipl myelom (MM), klonal plazma hücrelerinin kemik iliği infiltrasyonu ile karakterize hematolojik bir malignitedir. Günümüzde halen MM için tam kür elde edecek tedavi yoktur. IL-36; alfa, beta ve gama isimli üç agonistten oluşan bir sitokindir. İnflamasyondaki artışı literatürde kanıtlanmıştır. IL-17'nin ise inflamasyonla birlikte bazı romatolojik ve malign hastalıklarda rol oynadığı literatürde bildirilmiştir.

Yöntem: Bizim amacımız IL-36 ve IL-17'nin bilinmekte olan fizyolojilerinden yola çıkarak MM patogenezindeki rollerini anlayabilmek, yeni tedavi seçenekleri bulunabilmesi için literatüre katkı sağlamaktır.

Çalışmamıza 33 yeni tanı hiç tedavi almamış MM hastası ve 33 sağlıklı gönüllü alındı. Myelom hasta grubu ve sağlıklı grupta temel laboratuvar parametreleri, interlökin düzeyleri çalışmaya dahil edildi.

Bulgular: Çalışmamızda IL-36 alfa, beta, gama ve IL-17 düzeyi sağlıklı gruba göre hastalıklı grupta istatiksel olarak anlamlı şekilde düşük saptandı. IL-17 ölçümü ile beta-2 mikroglobulin arasında negatif yönlü bir ilişki bulduk. Bu nedenle IL-17 nin prognozu öngörmede bir belirteç olabileceğini düşündük.

Sonuç: Sonuç olarak, IL-36 ve IL-17'nin MM etiyopatogenezinde rolü olabileceğini, IL-36 alfa ve IL-17'nin prognoz ile ilişkili olabileceğini düşünüyoruz. Ancak daha geniş kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Multipl myelom, Interlökin 36, Interlökin 17

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How to Cite: Yıldız Bilge N, Terzi H, Doğan HO, Kablan D, Şencan M. Determination of Serum Interleukın-36 Alpha, Beta, Gamma and Interleukın-17 Levels in Patients with Multiple Myeloma. Cumhuriyet Medical Journal. 2024;46(1):57-65

Introduction

Multiple myeloma is a malignant neoplasm of plasma cells, that is characterized by the proliferation of bone marrow plasma cells and begins with an asymptomatic premalignant MGUS stage. It accounts for approximately 10% of hematologic malignant diseases.[1] The bone marrow stromal cell is a mononuclear, fibroblast-like cell that supports hematopoietic development. Adherence of MM cells activates the bone marrow stromal cells. Activation of the NF-kB pathway in stromal cells causes the secretion of proliferative, anti-apoptotic and chemotactic cytokines such as interleukin-6, stromal cell-derived factor-1 and insulin-like growth factor-1 and all of them directly support the continued adherence, growth and proliferation of MM cells.[2]

Interleukin-36 (IL-36) is a member of the IL-1 family and it is included three agonists (IL-36 alpha, beta, gamma), an antagonist (IL-Ra), a receptor (IL-36R) and an accessory protein (IL-36RAcP).[3] IL-36 is expressed in monocytes, T/B lymphocytes, spleen, bone marrow, tonsil, skin and lymph nodes.[4] In vitro and in vivo studies have shown that IL-36 and its receptor-mediated signaling mechanisms are involved in the processes governing fibrosis leading to organ failure or dysfunction. IL-36R is highly synthesized in the epithelial and skin cells and in the esophagus, thyroid, kidney, adrenal gland, and gallbladder.[5] However, it is observed that IL-36 mRNA is synthesized at the highest rate in keratinocytes.[6] IL-36 beta can stimulate its own synthesis and thanks to this feature, it is similar to the autocrine/paracrine cycle of IL-1. IL-17 and TNF are the molecules stimulating the synthesis of IL-36 alpha, IL-36 beta, and IL-36 gamma in keratinocytes. Various studies have also revealed that epidermal growth factor plays a role in the synthesis of IL-36 alpha and IL-36 beta in the skin. IL-36 gamma increase is triggered in the bronchial epithelium, which is exposed to intense inflammatory stimuli. High rates of IL-36 alpha and gamma are synthesized in the infected skin of the patients with psoriasis and in the lesioned skin of the patients with atopic dermatitis.[7]

IL-17 is a proinflammatory cytokine involved in the pathogenesis of autoimmune and inflammatory diseases together with various bacterial, fungal and viral infections.[8] IL-17 family has 6 forms (IL-17 A-F).[9] The interleukin-17 receptor (IL-17R) family consists of five members (IL-17R A to IL-17RE).[10] Recently, it is reported that IL-17C binds to IL-17RE and activates NF-kB.[11] The main targets of IL-17 are mesenchymal and myeloid cells.[12] IL-17 plays a role in the pathogenesis of diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory bowel diseases and psoriasis.[13] In addition, it takes also part in the pathogenesis of solid organ tumors such as cervix, esophagus, stomach, colorectal and hepatocellular cancer.[14]

The aim of the current study is to understand the possible roles of IL-36 and IL-17 in the pathogenesis of multiple myeloma and to contribute to the literature for new treatment options.

Materials and Methods

The present study was conducted with the approval of Sivas Cumhuriyet University Interventional Clinical Trials Ethics Committee (Decision No: 2022-02/01). The study was funded by Sivas Cumhuriyet University Scientific Research Projects (CÜBAP) with project number T-2022-973. In the study, 33 patients with MM, who accepted to Sivas Cumhuriyet University Faculty of Medicine Hematology Clinic, were newly diagnosed and had been never treated were included. The control group consisted of 33 volunteers, who were over 18 years of age, had no comorbidities and no regular medications, were not pregnant, were not smokers, had no active infection, had no diagnosed active malignancy, and no history of malignancy.

In the present study, the blood tests at the time of admission were used as routine blood tests. In the patient group, blood samples were taken at the time of diagnosis without receiving treatment. No blood samples were taken again during other stages of treatment. ISS (International Staging System) was used to determine the disease stages. The presence of bone fractures at the time of diagnosis was decided based on positron emission computed tomography (PET/CT), computed tomography and if any, magnetic resonance imaging reports.

During the study period, blood was collected from the peripheral vein of newly diagnosed MM patients and of the healthy control group into suitable tubes after at least eight hours of fasting for IL-36 alpha, IL-36 beta, IL-36 gamma, IL-17 levels and laboratory measurements. Serum IL-6 levels were also studied in the patient group from blood samples at the time of diagnosis. The blood samples were centrifuged at 2300g 4000 rpm for 10 minutes and stored in an Eppendorf tube at -80ºC. SunRed branded enzyme-linked immunosorbent assay (ELISA) kit was used for IL-36 alpha, IL-36 beta, IL-36 gamma, and IL-17 measurements.

Statistics

Data were analyzed with SPSS 27.0 program at confidence level of 95%. Mean, standard deviation (Mean±SD), minimum, maximum, median (M) statistics were given for the measurements. In the study, Mann Whitney/independent samples t-test was used the comparison of two groups, Kruskal Wallis/one-way ANOVA test for more than two groups, Chi-square test for the correlation between the grouped variables, and Pearson/Spearman correlation test for the correlation between numerical measurements. According to the results of normal distribution, t-test, ANOVA, and Pearson correlation tests were used for the normally distributed measurements and Mann Whitney U test was used for non-normally distributed measurements.

Results

Baseline Data

In the study, 33 MM patients and 33 healthy volunteers, who evaluated to Sivas Cumhuriyet University Faculty of Medicine Hematology Clinic, were included. In the MM patient group, 39.4% (n=13) were younger than 65 years of age and 60.6% (n=20) were over the age of 65. In the healthy

group, 66.7% (n=22) were under the age of 65 and 33.3% (n=11) were over the age of 65. In the MM patient group, 39.3% (n=13) were female and 60.6% (n=20) were male; while in the healthy group, 60.6% (n=20) were female and 39.4% (n=13) were male.

In the MM patient group, 30.3% (n=10) had IgG kappa type, 24.2% (n=8) had IgG lambda type, 6.1% (n=2) had IgA kappa type, 18.2% (n=6) had IgA lambda type, 12.1% (n=4) had kappa light chain myeloma, 6.1% (n=2) had lambda light chain myeloma, and 3% (n=1) had non-secretory type myeloma (Table 1).

Table 1. The Correlation of Clinical Characteristics with Gender in MM Patient Group

n(%)		Female	Male	Total	p
MM type	IgG kappa	7 (53.8)	3 (15)	10 (30.3)	
	IgG lambda	3 (23.1)	5 (25)	8 (24.2)	
	IgA kappa	0 (0)	2 (10)	2 (6.1)	
	IgA lambda	0 (0)	6 (30)	6 (18.2)	0.023*
	Kappa light chain myeloma	1 (7.7)	3 (15)	4 (12.1)	
	Lambda light chain myeloma	2 (15.4)	0 (0)	2 (6.1)	
	Non-secretory type myeloma	0 (0)	1 (5)	1 (3)	
Stage at the time of diagnosis (According to ISS)	Stage 1	3 (23.1)	3 (15)	6 (18.2)	
	Stage 2	3 (23.1)	6 (30)	9 (27.3)	0.799
	Stage 3	7 (53.8)	11 (55)	18 (54.5)	
Monoclonal gammopathy in blood immunofixation	Non-available	2 (16.7)	1 (5)	3 (9.4)	0.540
	Available	10 (83.3)	19 (95)	29 (90.6)	
Monoclonal gammopathy in urine immunoelectrophoresis	Non-available	0 (0)	5 (38.5)	5 (29.4)	0.261
	Available	4 (100)	8 (61.5)	12 (70.6)	
Bone involvement in PET at diagnosis	Non-available	1 (7.7)	5 (26.3)	6 (18.8)	0.361
	Available	12 (92.3)	14 (73.7)	26 (81.3)	
Fracture at diagnosis	Non-available	10 (76.9)	16 (84.2)	26 (81.3)	0.666
	Available	3 (23.1)	3 (15.8)	6 (18.8)	

At diagnosis, 54.5% (n=18) of the patients were in stage 3, 27.3% (n=9) patients in stage 2, and 18.2% (n=6) patients in stage 1. At the time of diagnosis, 81.3% (n=26) of the patients had bone involvement on PET/CT, and also 18.8% (n=6) patients had fractures (Table 1). A statistically significant correlation was found between gender and MM type groups in the MM patient group (p=0.023 <0.05). While the incidence of IgG kappa was higher in females (53.8%), the incidence of IgA lambda was higher in males (30.0%). The relationship of other clinical characteristics with gender was not significant (p>0.05) (Table 1).

Table 2 shows the treatments and treatment responses of the patients in the multiple myeloma group.

Comparison of Interleukin 36 alpha, Interleukin 36 beta, Interleukin 36 gamma and Interleukin 17 Levels with Other Parameters

There was a statistically remarkable difference between MM patient group and healthy group in terms of IL-36 alpha (p<0.001), IL-36 beta (p<0.001), IL-36 gamma (p<0.001), and IL-17 (p<0.001) measurements. IL-36 alpha (28.6 ng/L), IL-36 beta (17.89 ng/L), IL-36 gamma (22.63 ng/L), IL-17 (398.32 pg/ml) measurements were higher in the healthy group when compared to the MM patient group (Table 3).

There was a statistically remarkable difference between genders in the MM patient group in terms of IL-36 alpha (p=0.033 <0.05) measurements. IL-36 alpha (13.14 ng/L) was higher in men. The difference in other measurements was not statistically significant (p>0.05).

In the MM patient group, there was no statistically remarkable difference between those who responded to first- and second-line treatment and those who did not in terms of IL measurements (p>0.05). In this group, IL-36 beta measurements were higher in those who did not respond to third-line treatment and this difference was statistically significant **(p=0.029 <0.05)**. The difference was not remarkable for other IL measurements (p>0.05) (Table 4).

There was a negative, statistically remarkable correlation between IL-36 alpha measurement and albumin (r=-0.404, p=0.020<0.05) measurement in MM patient group. There was a negative, statistically remarkable correlation between IL-36 beta measurement and albumin (r=-0.410, p=0.018<0.05) measurement. Also, a negative, statistically remarkable correlation was found between IL-36 gamma measurement and platelet count (r=-0.400, p=0.021<0.05). There was a negative and statistically remarkable correlation between IL-17 measurement and beta2 microglobulin (r=0.389, p=0.025<0.05) measurement. The correlations between other measurements were not remarkable (p>0.05). There was a positive statistically remarkable correlation between IL-6 measurement and BUN (r=0.535, p<0.05) and a negative statistically remarkable correlation with albumin (r=-0.441, p<0.05) and lymphocyte count (r=-0.406, p<0.05).

Table 2. Treatment Characteristics in MM Patient Group

n (%)		Stage 1	Stage 2	Stage 3
First-line treatment	Drug-free follow up	2 (33.3)	0 (0)	0 (0)
	VCD	3 (50)	7 (87.5)	14 (77.8)
	Vel-dex	0 (0)	0 (0)	2 (11.1)
	MP	0 (0)	0 (0)	1 (5.6)
	AVD	1 (16.7)	1 (12.5)	1 (5.6)
First-line treatment response	Non-available	3 (100)	3 (37.5)	6 (42.9)
	Available	0 (0)	5 (625)	8 (57.1)
Receiving RT	Did not receive	4 (80)	8 (100)	10 (71.4)
	Received	1 (20)	0 (0)	4 (28.6)
ASCT	Not done	5 (100)	4 (50)	9 (64.3)
	Done	0 (0)	4 (50)	5 (35.7)
Second-line treatment	VCD	4 (80)	1 (20)	1 (8.3)
	Vel-dex	0 (0)	0 (0)	2 (16.7)
	Len-dex	1 (20)	2 (40)	6 (50)
	Lenalidomide	0 (0)	1 (20)	3 (25)
	VRD	0 (0)	1 (20)	0 (0)
Second-line treatment response	Non-available	2 (40)	2 (50)	6 (66.7)
	Available	3 (60)	2 (50)	3 (33.3)
ASCT after second-line treatment	Not done	1 (20)	2 (100)	8 (100)
	Done	4 (80)	0 (0)	0 (0)
Third-line treatment	MP	0 (0)	0 (0)	1 (16.7)
	Len-dex	2 (50)	0 (0)	1 (16.7)
	Len-dex+ixazomib	1 (25)	0 (0)	2 (33.3)
	CRD	0 (0)	1 (50)	0 (0)
	Daratumab	0 (0)	0 (0)	0 (0)
	Lenalidomide	1 (25)	1 (50)	0 (0)
	Vel-dex	0 (0)	0 (0)	1 (16.7)
	Pom-Dex	0 (0)	0 (0)	1 (16.7)
Third-line treatment response	Non-available	1 (25)	1 (100)	2 (66.7)
	Available	3 (75)	0 (0)	1 (33.3)
ASCT after third-line treatment	Not done	3 (75)	1 (100)	2 (66.7)
	Done	1 (25)	0 (0)	1 (33.3)

*p<0.05 means there is a significant correlation, p>0.05 means there is no significant correlation; Chi-square test (% according to both stage and MM type)
ASCT:Autologous stem cell transplantation, VCD:Bortezomib+Cyclophosphamide+Dexamethasone), Vel-dex:Bortezomib+ dexamethasone MP:Melphalan+prednisolone, AVD: Adriamisin+ Vincristine+Dexamethasone, len-dex:Lenalidomide+dexamethasone,VRD:Bortezomib+ Lenalidomide +Dexamethasone, CRD: Lenalidomide+bortezomib+Dexamethasone, Pom-Dex: Pomalidomid+Dexamethasone

Table 3. Comparison of Interleukin Clinical Measurements According to the Patient Groups

	Patient	Control	Test/p
Interleukin 36 alpha (ng/L)	11.55 (10.25-13.96)	23.44 (12.57-41.31)	U=195.0/ 0.000*
Interleukin 36 beta (ng/L)	4.22 (2.86-5.24)	14.57 (5.42-27.33)	U=180.0/ 0.000*
Interleukin 36 gamma (ng/L)	6.08 (4.88-6.93)	12.97 (7.31-36.77)	U=167.5/ 0.000*
Interleukin 17 (pg/ml)	94.82 (67.11-117.45)	298.29 (135.56-607.67)	U=105.0/ 0.000*

*p<0.05 means there is a significant correlation, Mann Whitney U test

Overall Survival Measurements

Overall survival: Minimum 1 month, maximum 23 months. In the patient group, 14 patients died and 19 patients are still being followed. There was a statistically remarkable difference between deceased and living patients in the MM patient group in IL-36 alpha and IL-6 measurements (p<0.05). IL-36 alpha and IL-6 measurements were higher in deceased patients. The difference was not remarkable for other IL measurements (p>0.05) (Table 5).

Table 4. Comparison of Interleukin Measurements in the MM Patient Group According to Response to Treatment Status

	First-line treatment		Test/p
	No Response	Response	
Interleukin 36 alpha (ng/L)	13.2 (10.25-15.24)	10.85 (9.61-14.26)	U=64.5/ 0.470
Interleukin 36 beta (ng/L)	4.08 (3.39-5.96)	3.9 (2.39-5.16)	U=68.0/ 0.611
Interleukin 36 gamma (ng/L)	6.65 (5.1-8.77)	6.46 (4.95-6.93)	U=63.0/ 0.437
Interleukin 6 (pg/ml)	9.94 (4.6-16.22)	11.9 (6.31-19.3)	U=65.0/ 0.503
Interleukin 17 (pg/ml)	96.39±32.71	94.68±26.59	t=0.144/ 0.886
	Second-line treatment		Test/p
	No Response	Response	
Interleukin 36 alpha (ng/L)	11.58 (10.14-14.89)	12.8 (11.5-15.6)	U=26.0/ 0.237
Interleukin 36 beta (ng/L)	3.69 (3.63-5.48)	4.3 (1.79-4.89)	U=36.0/ 0.611762
Interleukin 36 gamma (ng/L)	6.54 (5.88-7.77)	6.78 (4.89-7.07)	U=38.0/ 0.897
Interleukin 6 (pg/ml)	7.66 (3.9-15.46)	17.9 (4.57-21.95)	U=28.5/ 0.315
Interleukin 17 (pg/ml)	93.21±25.95	102.49±25.27	t=-0.762/ 0.457
	Third-line treatment		Test/p
	No Response	Response	
Interleukin 36 alpha (ng/L)	12.24 (9.94-15.60)	12.25 (10.62-14.78)	U=8.0/ 0.999
Interleukin 36 beta (ng/L)	4.34 (3.99-5.03)	3.76 (3.70-3.86)	U=0.0/ 0.029*
Interleukin 36 gamma (ng/L)	6.70 (4.79-8.54)	5.69 (4.83-9.18)	U=8.0/ 0.999
Interleukin 6 (pg/ml)	16.60 (7.33-23.35)	2.83 (1.89-5.03)	U=1.0/ 0.057
Interleukin 17 (pg/ml)	104.71±16.83	111.19±31.35	t=-0.364/ 0.728

*p<0.05 means there is a significant correlation, t/Mann Whitney U test

Discussion

Multiple Myeloma (MM) is a disease characterized by the accumulation of malignant clonal plasma cells in the bone marrow. It accounts for 1% of all cancers and 10% of hematologic cancers. The mean age at the time of diagnosis of myeloma reported in the literature is 69 years. During diagnosis, less than 3% of the patients are under the age of 40 years and 38% are 70 years and older .[1,15] In the present study, the mean age at the time of diagnosis was found to be 68.73±9.69 years, which is compatible with the literature. In addition, 39.4% (n=13) of the patients were under 65 years and 60.6% (n=20) were over 65 years .[16] However, in the present study, the mean age of the healthy group was remarkable lower than the mean age of the patient group. Due to the increase in comorbidities and susceptibility to infection with advancing age, it was difficult to find a healthy group at the old age group who met the inclusion criteria of being voluntary for the study, being over the age of 18, having no comorbidities or no regular medications, being non-pregnant, being non-smoker, having no active infection, having no diagnosed active malignancy, and having no history of malignancy. This is one of the limitations of the present study. In multiple myeloma, low albumin level is associated with poor prognosis. Since albumin induces cell growth stabilization and DNA replication with its antioxidant property, low albumin level affects prognosis negatively. There are also studies reporting a negative correlation between serum IL-6 level and serum albumin level in patients with myeloma .[17] The present study reported a statistically significant negative correlation between IL-6 level and albumin level which is compatible with the literature.

In the present study, a statistically significant difference was found between the MM patient group and the healthy group in terms of IL-36 alpha, IL-36 beta, IL-36 gamma, and IL-17 measurements. The mean values of IL-36 alpha (28.6 ng/L), IL-36 beta (17.89 ng/L), IL-36 gamma (22.63 ng/L), and IL-17 (398.32 pg/ml) measurements were higher in the healthy group when compared to the MM patient group. When IL levels were compared in terms of gender, IL-36 alpha (13.14 ng/L) measurement was higher in males. Also, in the MM patient group, IL-36 beta (4.46 ng/L) was higher in the patients who did not respond to third-line treatment when compared to the patients who responded. Although there is no data in the literature in this respect, we think that there is a need for further studies.

IL-36 has an important role in the etiopathogenesis of autoimmune, inflammatory, and malignant diseases such as psoriasis, chronic lung diseases, inflammatory bowel disease, rheumatoid arthritis, allergic rhinitis, Sjögren's syndrome and SLE. IL-36R is mostly expressed in the skin, gastrointestinal system, ovaries, lung, kidney, and lymphoid organs .[18-21] In the literature, studies aiming at understanding the action and synthesis mechanism of IL-36 have been mostly conducted in the field of dermatology and there are a limited number of studies on solid organ cancers and hematologic malignancies.

Johnston et al., demonstrated the role of IL-36 in pustular skin diseases in their study conducted in patients with pustular psoriasis.[22] There are literature information reporting that anakinra, an IL-1 receptor antagonist, and spesolimab, an IL-36 receptor blocker, are used in the treatment of generalized pustular psoriasis .[23,24]

Table 5. Comparison of Interleukin Measurements in MM Patient Group According to Living Status

	Living Status		Test/p
	Deceased	Living	
IL 36 alpha (ng/L)	13.49 (11.46-15.48)	10.26(9.79-12.74)	U=67.0/ 0.013*
IL 36 beta (ng/L)	5.05 (3.78-5.29)	3.72 (2.41-4.62)	U=89.0/ 0.100
IL 36 gamma (ng/L)	6.08 (5.14-8.01)	6.12 (4.81-6.74)	U=108.0/ 0.343
IL 6 (pg/ml)	17.40 (10.8-22.3)	9.26 (3.75-13.82)	U=71.5/ 0.020*
IL 17 (pg/ml)	101.76±35.16	91.44±26.13	t=0.967/ 0.341

*p<0.05 means there is a significant correlation, t/Mann Whitney U test, IL Interleukin

In their study, Al-Awaisi et al., demonstrated that IL-36 alpha, IL-36 beta and IL-36R expression increased with age in mouse heart. They reported that the damage caused by ischemia reperfusion decreased, blood flow improved, and neutrophil migration decreased with IL-36R antagonist administration and suggested that the agents targeting IL-36/IL36R pathway may be used in the treatment of ischemia reperfusion in older patients.[25]

When the solid organ cancers are examined, in their study conducted on the pathologic tissue cell culture of 20 patients with lung carcinoma, Backer et al., indicated that there was a significant increase in IL-36α, IL-36γ and IL-36R protein expression. They also revealed that stimulation of cancer cells with IL-36γ may increase the expression of the immune checkpoint protein PD-L1 (Programmed Death-Ligand 1).[26]

In the study conducted by Pan et al. with hepatocellular carcinoma cell culture; associated decreased intra-tumoral IL-36 alpha expression with poor prognosis and considered that IL-36 alpha may mediate anti-tumor immune responses by including CD3 and CD8 T lymphocytes in the tumor site and activating adaptive immunity.[27]

In their study, Chen et al., included the tumoral tissues of 185 patients with colorectal cancer, who had not received neoadjuvant chemotherapy, and 130 non-tumoral normal tissues and demonstrated that colonic IL-36 alpha, IL-36 beta, and IL-36 gamma significantly decreased in the patient group when compared to the matched non-colorectal carcinoma tissues. In the same study, patients with high IL-36 alpha level had a better survival. In IL-36 gamma, an opposite situation was found and patients with low IL-36 gamma levels had higher survival rates.[28] In their previous study, Pan et al., thought that IL-36 alpha showed anti-tumor effect by activating adaptive T-cell immune responses in colorectal carcinoma.[27] A negative correlation between IL-36 alpha measurement and albumin level (r=-0.404, p=0.020 <0.05) in the MM patient group and the higher IL-36 alpha measurement (13.76 ng/L) in deceased patients when compared to living patients in the myeloma patient group in the present study suggest that IL-36 alpha may be associated with prognosis. However, no significant correlation was found between overall survival and IL levels. It is considered that this may be caused by the insufficient number of patients and further clinical studies are needed.

In their study, Wang et al., found that IL-36 gamma supported directly the effector exchange of type 1 lymphocytes in vitro and showed a strong anti-tumor immune response in vivo.[29] In their study, Chen et al., revealed the anti-tumorigenic role of IL-36 gamma in a breast cancer cell line. Via the application of IL-36 gamma-expressing plasmid and doxorubicin together to breast carcinoma cell lines, it was shown that IL-36γ and doxorubicin-loaded micelles remarkable reduced the metastasis.[30]

In contrast to these data, Le et al., reported that IL-36 gamma showed pro-tumorigenic effect by stimulating extracellular signal-regulated kinase (ERK) 1/45 activation in their study on gastric cancer.[31]

In the literature, it has been reported that IL-36 cytokine family shows both pro-tumorigenic and anti-tumorigenic activity in various cancer types. It is thought that more extensive molecular studies are required to resolve this dilemma and to further clarify the etiopathogenesis.

It is known that leukemic progenitor cells infiltrating the bone marrow in acute myeloid leukemia express more IL-36 than normal hematopoietic progenitor cells.[32]

In their in-vivo mouse epidermis and in-vitro primary human keratinocyte culture studies, Carrier et al., demonstrated that IL-36s were not only regulated by Th17 cytokines but they can also regulate the expression of Th17 cytokines themselves .[33]Under the light of this information, IL-17 blockers have taken their place in the treatment of dermatologic diseases. Also, even secukinumab, which is an IL-17A monoclonal antibody, was approved for the treatment of moderate/severe psoriasis in 2015. [34]

In their study, Chiricozzi et al., reported that IL-17/TNF-α interactions were present not only in epidermal keratinocytes but also in some leukocytes. [35] The relationship between chronic inflammation and cancer has been previously reported in the literature. It is suggested that approximately 15% of all human cancers are caused by infection and chronic inflammation.[36] IL-17 is a proinflammatory cytokine proven to be effective in the development of prostate, colon, skin, breast, lung and pancreatic cancers .[37-42] In their study, Zhang et al., showed that IL-17 played a role in the pathogenesis of prostate cancer. In line with these results, they stated that IL-17 is a potential target for developing new strategies in the prevention and treatment of prostate cancer.[43]

In the literature, there are reports stating that IL-17 has both pro-tumorigenic and anti-tumorigenic roles [44]. In their study, Kryczek et al., reported that IL-17 ectopically expressed in tumor cells suppressed tumor progression through increased anti-tumor immunity in immune-competent mice and stimulated tumor progression through increased inflammatory angiogenesis in immune-suppressive mice.[45]

Novitskiy et al., conducted a study on breast carcinoma cells and revealed that IL-17, secreted by Th17 cells, caused a tumor-progressing effect by increasing the pro-tumorigenic characteristics of myeloid cells.[40]

On the contrary, Chen et al., conducted a study on 192 patients with gastric adenocarcinoma and found that the patients with high IL-17 levels had remarkably higher five-year survival rate than those with low levels .[46] Benchetrit et al., carried out a study by transplanting hematopoietic tumors (plasmacytoma and mastocytoma) into immunocompetent mice and reported that IL-17 inhibited the tumor growth rate and the pro-tumor or anti-tumor effects of IL-17 on tumor development was associated with immunity.[47]

Bankır et al., compared the median levels of serum IL-17 and IL-23 in the patients with early-stage chronic lymphocytic leukemia (CLL) with the healthy control group and found no statistically significant difference. They reported that this may be caused by the result of the early stage of the patients.[48]

In the study conducted by Tang et al., on the patients with CLL; all of IL-6, IL-17 and IL-23 levels were found to be significantly higher in the serum samples of CLL patients; whereas, TGF-β1 and IL-10 concentrations were much lower than the controls. They suggested that this situation was due to the fact that the normal cytokine microenvironment was damaged in CLL. The median IL-17 level in the patients with CLL in that study was found to be 3.23 pg/mL, which is significantly lower than the levels in the present study.[49]

In their study, Alexandrakis et al., compared serum IL-17 levels of 40 myeloma patients who had never received any treatment with a healthy control group; however, they found no statistically significant difference. [50] In the present study, no statistically significant difference was found in IL-17 measurements between the stage groups in the MM patient group.

In their study, Lemancewicz et al., compared IL-17A and IL-17E levels in 34 patients with newly diagnosed myeloma with the healthy group and found that IL-17E levels were significantly higher in the myeloma group. As a result, they concluded that IL-17 may both stimulate and suppress tumor growth and there is a balance between the effects of IL-17A and IL-17E and they emphasized that more comprehensive studies are needed .[51]

Consequently, even though the role of IL-36 and IL-17 in dermatologic diseases is more clearly understood, it is thought that they may have a role in the etiopathogenesis of solid organ cancers and hematologic malignancies. When the literature data is examined, this issue has not yet been clarified. The use of IL-36 and IL-17 blocks in the treatment in dermatology arouses curiosity in terms of new options for myeloma treatment. In addition, it may be useful in predicting prognosis in myeloma depending on the studies conducted on solid organ cancers in the literature. Therefore, it is thought and recommended to conduct further comprehensive molecular studies in myeloma.

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CMJ. 2024;46(1):66-73
DOI: 10.7197/cmj.1351473

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

After the Earthquakes with Epicenter in Kahramanmaraş on February 6, 2023; Crush Syndrome

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Research Article

History

Received: 28/08/2023
Accepted: 19/03/2024

This study was reported as an oral presentation at the 12th International Participatory Current Kidney Diseases, Hypertension and Transplantation Congress (12th International Participatory Current Kidney Diseases Hypertension and Transplantation Congress: Update 2023, April 26-30, 2023, Sapanca, SS-02, Page: 63).

ABSTRACT

Objective: One of the vital problems after earthquakes that caused many deaths and injuries is crush syndrome due to traumatic muscle damage. The aim of this study was to determine the clinical course of patients with crush syndrome and identify factors that may be associated with crush syndrome.
Methods: After the two earthquakes of 7.7 and 7.6 magnitude affecting 11 provinces with the epicentre in Kahramanmaraş on 6 February 2023, 319 patients over the age of 18 were admitted to our hospital between 6-14 February. 87 of 319 patients received inpatient follow-up and treatment. The age, gender, duration of stay in the rubble, province of residence, operation performed, duration of hospital stay, amount of fluid given in the first 24 hours, amount of urine output in the first 24 hours, body trauma sites, some laboratory parameters at the time of admission and during follow-up were retrospectively evaluated from the hospital records of all 43 patients diagnosed with crush syndrome among the inpatients between 6-28 February.
Results: The age of the patients was 39±19.6 years, duration of stay under the cave-in(hours) 22.74±36.32, duration of hospitalization(days) 7.26±5.42, amount of fluid given in the first 24 hours(ml) 4954.18±3142, amount of urine output in the first 24 hours(ml) 2646.42±2262.65, admission creatinine(mg/dl) 1.59±2.25, admission creatine kinase(CK)(U/L) 11716.37±18520. 44.2% of the patients were female, 72.1% came from Kahramanmaraş province, 46.5% underwent surgical intervention, 67.4% had an admission CK above 1000 u/l, 14% received hemodialysis treatment and 51.2% had a duration of hospitalization longer than 21 days.
The effect of other parameters on the duration of hospitalization and the time to reach the reference range of CK and correlation with laboratory parameters were analysed.
Conclusion: As a result, it is thought that the parameters affecting the time to reach the CK reference range and the duration of hospitalization can be used to calculate and reduce the duration of hospitalization in prospective crush syndrome cases.

Keywords: Crush Syndrome, Earthquake, Traumatic Rhabdomyalysis

6 Şubat Kahramanmaraş Merkezli Depremler Sonrası Crush Sendromu

Araştırma Makalesi

Süreç

Geliş: 28/08/2023
Kabul: 19/03/2024

ÖZET

Amaç: Çok sayıda ölüm ve yaralanmaya neden olan depremler sonrasında hayati sorunlardan biri de travmatik kas hasarına bağlı meydana gelen crush(ezilme) sendromudur. Bu çalışmada crush sendromu gelişmiş hastaların klinik seyirlerini ve crush sendromu ile ilişkili olabilecek faktörleri saptanması amaçlandı.
Yöntem: 6 Şubat 2023 tarihinde 11 ilde etkili olan Kahramanmaraş merkezli 7.7 ve 7.6 büyüklüğündeki iki depremin ardından 6-14 Şubat tarihleri arasında hastanemize 18 yaş üstü 319 hasta başvurdu. 319 hastanın 87'i yatarak takip ve tedavi aldı. Yatarak tedavi alan hastalardan Crush sendromu tanısı alan 43 hastanın tamamının 6-28 Şubat arasındaki hastane kayıtlarından yaşı, cinsiyeti, geldiği ili, enkazda kalış süresi, yapılan operasyon, hastanede yatış süresi, ilk 24 saate verilen mayii miktarı, ilk 24 saat idrar çıkımı miktarı, travma yerleri, hastaneye başvuru esnasında ve takibindeki bazı laboratuvar parametreleri geriye dönük değerlendirildi.
Bulgular: Hastaların yaşı 39±19.6 yıl, enkazda kalış süresi(saat) 22,74±36.32, hastane yatış süresi(gün) 7,26±5,42, ilk 24 saatte aldığı mayi(ml) 4954,18±3142, ilk 24 saat idrar miktarı(ml) 2646,42±2262,65, başvuru kreatinin(mg/dl) 1,59±2,25, başvuru kreatin kinaz(u/l) 11716,37±18520 olarak saptandı.
Hastaların %44,2'i kadın, %72,1'i Kahramanmaraş ilinden gelmiş, %46,5'una cerrahi müdahale yapılmış, %67,4'ünün başvuru CK 1000 u/l'nin üzerinde, %14'üne hemodiyaliz tedavisi uygulanmış, %46,5'inde CK referans aralığına gelme süresi 7 günden kısa, %51,2'inde yatış süresi 21 günden uzun saptandı.
Yatış gün süresi, CK referans aralığına gelme süresi üzerine diğer parametrelerin etkisi ve laboratuvar parametreleri ile korelasyonu analiz edildi.
Sonuç: Sonuç olarak CK referans aralığına gelme süresini ve hastanede yatış süresini ön görmede süreye etkili parametreler değerlendirilerek ileriye dönük crush sendromu olgularında hastanede yatış süresini hesaplamada ve azaltmada kullanılabileceği düşünülmektedir.

Anahtar Kelimeler: Crush Sendromu, Deprem, Travmatik Rabdomiyaliz

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How to Cite: Aşkın MF, Taştemur Ş, Gedikli MA, Candan F, Koç Y. Crush Syndrome After 6 February Kahramanmaraş Centered Earthquakes, Cumhuriyet Medical Journal. 2024;46(1):66-73

Introduction

On February 6, 2023, at 04:17 and 13:24 in Turkiye time, two major earthquakes with epicentres in Pazarcık (Kahramanmaraş) and Elbistan (Kahramanmaraş), with magnitudes of 7.7 and 7.6, respectively, affected 11 provinces (Adana, Adıyaman, Diyarbakır, Elazığ, Gaziantep, Hatay, Kahramanmaraş, Kilis, Malatya, Osmaniye, Şanlıurfa).

Earthquakes have caused great destruction in settlements for centuries. It is a natural disaster that affects public health to a great extent and in a multi-layered way due to both the deaths and injuries it causes. Crush syndrome, which occurs due to traumatic muscle damage that is vital after an earthquake, is an issue that should be emphasised sensitively.

Crush syndrome was first reported by Seigo in 1923 with his study on three soldiers who lost their lives during World War I. In 1941, it was defined in a study conducted by Bywaters on those who died after the aerial bombardment of London by the Germans.[1]

Crush syndrome is a systemic disease characterized by the release of cellular contents (uric acid, phosphate, potassium, etc.) into the bloodstream due to muscle damage resulting from the crushing of muscle-rich body regions. It can lead to acute kidney injury and multiple organ dysfunction.[2]

The aim of this study was to determine the clinical course of patients with crush syndrome who were hospitalised in our hospital after the earthquakes centred in Pazarcık (Kahramanmaraş) and Elbistan (Kahramanmaraş) and to determine the factors that may be related to crush syndrome.

Materials and Methods

All patients aged 18 years and above who were admitted to our hospital between February 6 and February 14, from the earthquake zone and hospitalised with the diagnosis of crush syndrome were included in the study. The age, gender, city where the earthquake occurred, duration of stay in the rubble, amount of parenteral fluid given in the first 24 hours after extraction from the rubble, amount of urine in the first 24 hours, trauma sites, surgical interventions if performed, and length of hospital stay of the patients who were hospitalized due to crush syndrome, laboratory parameters (blood urea nitrogen (BUN), creatinine, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), lactate dehydrogenase (LDH), potassium, phosphorus, sodium, calcium, C-reactive protein (CRP), white blood cell (WBC), hemoglobin, platelets) during admission and follow-up were recorded.

Clinical course, the requirement for dialysis, and any interventions such as fasciotomy, if any, were recorded from the patient files. The creatine kinase (CK) levels of all patients were divided into 5 groups (170-500; 500-1000; 1000-5000; 5000-10000; >10000), and factors associated with CK levels exceeding 5000 were investigated. Patients were also grouped according to the length of hospital stay (1-7 days, 8-14, 14-21 and >21 days) and factors that may be associated with prolonged hospitalization were determined.

The data obtained from our statistical method study is loaded into the SPSS 22.0 program and in the evaluation of the data, when the parametric test assumptions are fulfilled (Shapiro-Wilk), when comparing the measurements obtained from the same individuals at different times, variance analysis in repeated measurements, the least significant difference method to find the measurement groups that make a difference as a result of the analysis, Pearson-Spearman correlation coefficient was found to determine the relationship between the variables, and the Chi Square test was applied to evaluate the data obtaied by counting. Our data were stated in the tables as arithmetic mean, standard deviation, number of individuals and percentage, and the error level was accepted as 0.05.

Results

A total of 319 patients, including 174 female, were admitted to the hospital between February 6 and February 14 2023. While 13 of the 319 patients refused treatment and left the emergency department, 218 patients were treated as outpatients and discharged with recovery, 1 patient died right after he came to the emergency department and the remaining 87 patients were hospitalized and treated. It was found that 43 of 87 those patients had a diagnosis of crush syndrome.

Of the 43 patients diagnosed with crush syndrome, 19 were female. Clinical characteristics and laboratory parameters of patients with crush syndrome are shown in Table 1 and Table 2. The majority of the patients (72.1%) were from Kahramanmaraş province. 88.4% of the patients were followed up in the clinics. Fasciotomy and amputation were performed on 16.3% and 9.3% of the patients, respectively, and no surgical intervention was required in 53.5% of the patients. When the trauma sites of the patients were classified as head, chest, lower extremity, upper extremity and abdomen, 55.8% had 1 site injury, 23.3% had 2 site injuries and 20.9% had 3 site injuries. It was found that 39.5% of the patients stayed in the rubble for 2-6 hours. When admission CK levels were analysed, 27.9% of the patients had CK levels above 10.000 U/L. In 46.5% of the patients, CK reached the reference range in less than 7 days. The total amount of fluid (oral and intravenous) given to the patients in the first 24 hours was between 5000-10.000 ml in 34,9% of the patients. The amount of urine excreted in the first 24 hours was between 500-3500 ml in 55.8% of the patients and less than 500 ml in 16.3%. Hemodialysis treatment was applied to 14% of the patients.

Table 1. Clinical Characteristics and Laboratory Parameters of Patients with Crush Syndrome

		n	%
Gender	Male	24	55.8
	Female	19	44.2
Province	Adıyaman	3	7.0
	Gaziantep	1	2.3
	Hatay	3	7.0
	Kahramanmaraş	31	72.1
	Malatya	5	11.6
Place of hospitalization	Clinic	38	88.4
	Intensive Care Unit	5	11.6
Surgical intervention	None	23	53.5
	Amputation	4	9.3
	Fasciotomy	7	16.3
	Fracture operation	4	9.3
	Tube Thoracostomy	3	7.0
	Other	2	4.7
Number of trauma sites	1	24	55.8
	2	10	23.3
	3	9	20.9
CK level on admission (U/L)	170-500	4	9.3
	500-1000	10	23.3
	1000-5000	9	20.9
	5000-10000	8	18.6
	+10000	12	27.9
Time to reach CK Reference Range (days)	1-7	20	46.5
	8-14	7	16.3
	15-21	8	18.6
The first 24 hours of fluid taken (ml)	0-2500	12	27.9
	2500-5000	12	27.9
	5000-10000	15	34.9
	>10000	4	9.3
The first 24 hours of urine excreted (ml)	0-500	7	16.3
	500-3500	24	55.8
	3500-10000	12	27.9
Hemodialysis	Performed	6	14.0
	Not performed	37	86.0
Duration of stay in the rubble (hours)	0-1	8	18.6
	2-6	17	39.5
	7-24	10	23.3
	+24	8	18.6
Duration of hospitalization (days)	1-7	11	25.6
	8-14	6	14.0
	15-21	2	4.7
	>21	22	51.2

The minimum, maximum, mean and standard deviation values of the patients' age, duration of stay in the rubble, the amount of fluid taken in the first 24 hours, the amount of urine excreted in the first 24 hours, the time to reach the CK reference range, the duration of hospitalization, and the admission laboratory parameters are given in detail in Table 2

Table 2. Clinical and Laboratory Parameters on Admission and Their Quantitative Results

	n	Min	Max	Mean	SD	Reference Values
Age	43	18	97	39.09	19.66	
Duration of stay in the rubble (hours)	40	0	120	22.74	36.32	
The first 24 hours of fluid taken (ml)	43	750	10600	4954.18	3142.61	
The first 24 hours of urine excreted (ml)	43	0	9600	2646.62	2262.65	
Time to reach CK Reference Range (days)	35	1	21	8.71	5.98	
Duration of hospitalization (days)	19	1	20	7.26	5.42	
BUN (mg/dl)	43	3.90	109.90	27.56	23.36	6-20
Creatinine (mg/dl)	43	0.29	11.01	1.59	2.25	0.7-1.2
Albumin (mg/dl)	7	23.20	35.70	28.37	4.89	35-52
ALT (u/l)	43	14	673	120.51	140.12	0-41
AST (u/l)	43	21	1661	221.09	322.38	0-40
CK (u/l)	43	274	90000	11716.37	18520.60	0-190
LDH (u/l)	40	209	4159	673.75	696.80	135-225
Potassium (mmol/l)	43	2.95	6.50	4.33	0.78	3.5-5.1
Phosphorus (mg/dl)	38	1.42	7.93	3.72	1.85	2.5-4.5
Magnessium (mg/dl)	5	1.68	2.18	1.97	0.20	1.6-2.6
Sodium (mmol/l)	43	127	149	138.76	4.67	136-145
Calcium (mg/dl)	43	6.19	10.17	8.28	0.96	8.6-10.2
CRP (mg/l)	32	0.63	349.94	96.33	91.01	0-5
WBC (10^9/L)	43	5.89	69.25	13.48	9.94	4-10.5
Hemoglobin (g/dl)	43	7.30	18.10	11.55	2.17	13.5-18
Platelets (10^9/L)	43	94	366	215.97	60.75	150-450

Table 3. Comparison of Duration of Hospitalization (days) with Other Parameters

		1-7 days	8-14 days	15-21 days	>21 days	p
		n(%)	n(%)	n(%)	n(%)	
Province	Adıyaman	3(100)	0(0)	0(0)	0(0)	
	Gaziantep	0(0)	0(0)	0(0)	1(100)	
	Hatay	2(66.7)	1(33.3)	0(0)	0(0)	0.020*
	Kahramanmaraş	4(13.8)	5(17.2)	1(3.4)	19(65.5)	
	Malatya	2(40)	0(0)	1(20)	2(40)	
CK on admission (U/L)	170-500	4(100)	0(0)	0(0)	0(0)	
	500-1000	2(25)	2(25)	0(0)	4(50)	
	1000-5000	2(22.2)	3(33.3	1(11.1)	3(33.3)	<0.01*
	5000-10000	3(37.5)	1(12.5)	0(0)	4(50)	
	+10000	0(0)	0(0)	1(8.3)	11(91.7)	
Number of trauma sites	1	10(41.7)	2(8.3)	0(0)	12(50)	
	2	0(0)	1(10)	1(10)	8(80)	<0.01*
	3	1(14.3)	3(42.9)	1(14.3)	2(28.6)	
Surgical intervention	None	8(34.8)	5(21.7)	1(4.3)	9(39.1)	
	Amputation	0(0)	1(25)	0(0)	3(75)	
	Fasciotomy	0(0)	0(0)	0(0)	7(100)	
	Fractur operation	1(25)	0(0)	1(25)	2(50)	0.104
	Tube Thoracostomy	0(0)	0(0)	0(0)	1(100)	
	Other	2(100)	0(0)	0(0)	0(0)	
Duration of stay in the rubble (hours)	0-1	4(50)	0(0)	1(12.5)	3(37.5)	
	2-6	6(40)	1(6.7)	0(0)	8(53.3)	0.082
	7-24	0(0)	3(30)	1(10)	6(60)	
	+24	1(12.5)	2(25)	0(0)	5(62.5)	
The first 24 hours of fluid taken (ml)	0-2500	3(25)	2(16.7)	0(0)	7(58.3)	
	2500-5000	3(25)	1(8.3)	1(8.3)	7(58.3)	0.382
	5000-10000	2(15.4)	2(15.4	1(7.7)	8(61.5)	
	>10000	3(75)	1(25)	0(0)	0(0)	
The first 24 hours of urine excreted (ml)	0-500	0(0)	2(28.6)	0(0)	5(71.4)	
	500-3500	7(30.4)	3(13)	2(8.7)	11(47.8)	0.514
	3500-10000	4(36.4)	1(9.1)	0(0)	6(54.5)	
Time to reach CK Reference Range (days)	1-7	7(38.9)	3(16.7)	1(5.6)	7(38.9)	
	8-14	1(14.3)	1(14.3)	0(0)	5(71.4)	0.139
	15-21	0(0)	0(0)	1(12.5)	7(87.5)	

Regarding the duration of hospitalization, 25.6% of the patients were hospitalized between 1-7 days, 14% between 8-14 days, 4.7% between 15-21 days, while the majority (51.2%) were hospitalized for more than 21 days and 2 patients were exited during this period. While 19 of 29 patients from Kahramanmaraş province were hospitalized for more than 21 days, all 3 patients from Adıyaman province and 2 of 3 patients from Hatay province were hospitalized for less than 7 days. Of the 12 patients with a CK level of 10,000 U/L and above measured at the time of admission, 11 had a hospitalization period of more than 21 days, while all 4 patients with a CK level between 170-500 U/L had a hospitalization period of less than 7 days. Half of 24 patients with one trauma site were hospitalized for more than 21 days and 10 for less than 7 days; 8 of 10 patients with 2 trauma sites were hospitalized for more than 21 days; 2 of 7 patients with 3 trauma sites were hospitalized for more than 21 days and 3 for 8-14 days. All 7 patients who underwent fasciotomy and 3 of 4 patients who underwent amputation were hospitalized for more than 21 days and there was no significant difference between surgical intervention and length of hospitalization. There was no significant difference between the amount of fluid (oral and intravenous) taken in the first 24 hours and the amount of urine excreted in the first 24 hours and the length of hospitalization. There was no significant difference between the time required for the CK level to decrease to the normal reference range and the duration of hospitalization. Detailed analysis is shown in Table 3.

Patients were divided into two groups according to the CK levels at the time of admission. 23 patients had CK levels <5000 U/L and the remaining 20 patients had CK levels >5000 U/L at admission (Table 4). There was no significant difference between the CK levels of the patients on admission and the province of origin (p=0.473), number of trauma sites (p=0.708), place of hospitalization (p=0.755), length of stay in the rubble (p=0.159), first 24 hours of fluid intake (p=0.7), and first 24 hours of urine volume (p=0.56). When compared with surgical intervention, CK levels were below 5000 U/L in 16 of 23 patients who had no surgery, above 5000 U/L in 3 of 4 patients who underwent amputation, and above 5000 U/L in all 7 patients who underwent fasciotomy and was statistically significant (p<0.01*). 17 of 20 patients with a CK reference range of less than 7 days had a CK level below 5000 U/L, 5 of 7 patients with a range of 8-14 days had a CK level above 5000 U/L, and all 8 patients with a range of 15-21 days had a CK level above 5000 U/L, which was statistically significant (p<0.01*). All 6 patients who underwent hemodialysis had admission CK levels above 5000 U/L and 27 of 37 patients who did not have hemodialysis had admission CK levels below 5000 U/L, which were statistically significant (p<0.01*).

Table 4. Comparison of CK Levels at Hospital Admission with Other Parameters

		<5000 U/L	>5000 U/L	p
		n(%)	n(%)	
Province	Adıyaman	3(100)	0(0)	
	Gaziantep	0(0)	1(100)	
	Hatay	2(66.7)	1(33.3)	0.473
	Kahramanmaraş	15(48.4)	16(51.6)	
	Malatya	3(60)	2(40)	
Number of trauma sites	1	12(50)	12(50)	
	2	5(50)	5(50)	0.708
	3	6(66.7)	3(33.3)	
Place of hospitalization	Clinic	20(52.6)	18(47.4)	0.755
	Intensive Care Unit	3(60)	2(40)	
Surgical intervention	None	16(69.6)	7(30.4)	
	Amputation	1(25)	3(75)	
	Fasciotom	0(0)	7(100)	<0.01*
	Fractur operation	2(50)	2(50)	
	Tube Thoracostomy	3(100)	0(0)	
	Other	1(50)	1(50)	
Duration of stay in the rubble (hours)	0-1	7(87.5)	1(12.5)	
	2-6	9(52.9)	8(47.1)	0.159
	7-24	4(40)	6(60)	
	>24	3(37.5)	5(62.5)	
The first 24 hours of fluid taken (ml)	0-2500	5(41.7)	7(58.3)	
	2500-5000	8(66.7)	4(33.3)	0.70
	5000-10000	8(53.3)	7(46.7)	
	>10000	2(50)	2(50)	
The first 24 hours of urine excreted (ml)	0-500	1(14.3)	6(85.7)	
	500-3500	16(66.7)	8(33.3)	0.56
	3500-10000	6(50)	6(50)	
Time to reach CK Reference Range (days)	1-7	17(85)	3(15)	
	8-14	2(28.6)	5(71.4)	<0.01*
	15-21	0(0)	8(100)	
Hemodialysis	Performed	0(0)	6(100)	<0.01*
	Not performed	23(62.2)	14(37.8	

In the analysis of 21-day laboratory data, when CK level was compared with surgical intervention, it was found that 75% of the patients who did not undergo surgery and all of the patients who underwent tube thoracostomy reached the reference range in 1-7 days, 66.7% of the patients who underwent fasciotomy and all of the patients who underwent amputation reached the reference range in 15-21 days and a statistically significant difference was found (p<0.01*).

No significant difference was found between the time to reach the CK reference range and the number of trauma sites (p=0.904), place of hospitalization (p=0.801), province of origin (p=0.472), gender (p=0.082), length of stay in the rubble (p=0.144), hemodialysis treatment (p=0.076), fluid intake in the first 24 hours (p=0.758), and urine output in the first 24 hours (p=0.150).

When urine output was compared with the amount of fluid taken in the first 24 hours, 33% of patients who received less than 2500 ml of fluid had urine output below 500 ml, 15.8% of patients who received more than 5000 ml of fluid had urine output below 500 ml, 47.4% of patients who received more than 5000 ml of fluid had urine output above 3500 ml and a statistically significant difference was found (p<0.01*).

There was no statistically significant difference in urine output in the first 24 hours between patients admitted to the intensive care unit and patients admitted to the clinic (p=0.825). We did not find any statistically significant difference between urine output in the first 24 hours and length of stay in the rubble (p=0.502).

There was no statistically significant difference between the duration of stay in the rubble and the province of origin of the patients (p=0,195).

Of 38 patients admitted to the clinic, 60.5% had single site injuries and 60% of 5 patients admitted to the intensive care unit had 3 site injuries and a statistically significant difference was found (p=0.045*) There was no statistically significant difference between the number of trauma sites and the length of stay in the rubble (p=0.798)

Hemodialysis treatment was given to 5 of 7 patients with urine output below 500 ml and one of 24 patients with urine output between 500 ml and 3500 ml in the first 24 hours, and hemodialysis treatment was not given to any of the 12 patients with urine output above 3500 ml, and a statistically significant difference was found (p<0.01*).

Surgical intervention was not performed in 57.9% of the patients admitted to the clinic and 20% of the patients admitted to the intensive care unit and a statistically significant difference was found (p=0.22*).

4.2% of patients with single site injuries, 10% of patients with 2 site injuries, 33.3% of patients with 3 site injuries were hospitalized in intensive care unit and a statistically significant difference was found (p=0.042*).

There was no statistically significant difference between surgical intervention and number of trauma sites (p=0.55).

The duration of hospital stay and sodium level (r=-.640; p=0-.03), hemoglobin level (r=-.466; p=.044), and time to reach CK reference range (r=.653; p= ,011) was found to be correlated. A correlation was found between the duration of stay in the rubble and ALT (r=.423; p=.007), AST (r=.473; p=.002), CK (r=.468; p=.002), phosphorus (r=-.464 ; p=.005), calcium (r=-.532; p<0.001), WBC (r=.407; p=.007), first 24 hours urine amount (r=-.392; p=.009) time to reach the CK reference range (r=.394; p=.019) and those who underwent fasciotomy (r=.343 p=.03).

BUN (r=.394; p=.019) ALT (r=.683; p<.001), AST (r=.835; p<.001), CK (r=.847) with time to reach CK reference range ; p<.01), LDH (r=.719; <.001), potassium (r=-.386; p=.022), sodium (r=-.353; p=0-.038), calcium (r=-.674; p<0.001) and WBC (r=.334; p=.05) were correlated. The amount of urine excreted in the first 24 hours and BUN (r=-.392; p=.009), creatine (r=-.445; p=.003), ALT (r=-.372; p=.014), CK (r=-.308; p=.044) levels were found to be correlated. Hemodialysis patients and BUN (r=.685; p<.01), ALT (r=.594; p<.01), AST(r=.549; p<.01), CK (r=.657; p<.01), creatine (r=.71; p<.01), LDH (r=597; p<.01), phosphorus (r=807; p<.01), sodium (r=-.445 ; p=0.03), WBC (r=.407; p=.007), amount of urine output in the first 24 hours (r=-.467; p<.01), time to reach CK reference range (r=.358 ; p=.044) were also correlated.

Discussion

Earthquakes can cause mass mortality and morbidity. Turkey is located on the Mediterranean Alp-Himalayan seismic belt, which is one of the most active seismic belts in the world.[3] Therefore, many earthquakes have occurred in our country from past to present, which have caused many deaths and injuries. In our study, it was aimed to understand whether there is a relationship between crush syndrome, which is one of the most important problems after the earthquake, and certain parameters and to contribute to the medical literature.

In the two earthquakes that occurred on the same day, both centered in Kahramanmaraş, harsh climatic conditions and transportation problems made search and rescue activities challenging. The duration of patients' stay in the rubble was higher in our study (22.7+-36.3 hours) than in Marmara (11.7 ± 14.3 hours), Kobe (9 ± 13 hours) and Erzincan (9 ± 5 hours).[4,5] Michaelson suggested that the pressure applied to the muscles must last longer than four hours for crush syndrome to develop, it is also known that crush syndrome also develop in patients who were immediately rescued from the rubble.[6]

One of the expected risk factors for crush syndrome is the duration of stay under rubble. In our study, higher ALT, AST, CK, phosphorus, WBC levels and lower calcium levels were found in patients with longer duration of stay under rubble. Sagheb et al. found that the requirement for hemodialysis increased as the duration of stay under rubble increased in their study conducted after the Bam earthquake, and Sever et al. found that those who stayed under rubble for a shorter time the requirement of hemodialysis increased compared to those who stayed under rubble for a longer time in their study conducted after the Marmara earthquake.[5,7] In our study, no

significant difference was found between hemodialysis and duration of stay under rubble.

The mean CK level was 11.716±18.520 (274-90000) U/L. The mean CK level at admission was lower than the Marmara earthquake (58.205 U/L) and Kobe earthquake (66.504 U/L) and higher than the Wenchuan earthquake (5260 U/L) and Iran earthquake (2975 U/L).[8–11]

CK levels above 5000 U/L were found in all 7 patients who underwent fasciotomy, suggesting that it is related to the severity of muscle destruction. A direct correlation between the severity of muscle destruction and CK level is an expected finding.[12]

In our study, as in the study of Sever et al. after the Marmara earthquake, a positive correlation was found between the time under rubble and fasciotomy.[13] Our study supports the hypothesis of Sever et al. that patients with extremity trauma (compared to those with thorax, abdomen and head trauma) may survive longer under rubble, but since their injuries were not treated in the early period, they are at a higher risk of experiencing a more severe compartment syndrome and requiring fasciotomy and amputation.[13]

Duman et al. thought that early fasciotomy would have favorable results on mortality and morbidity.[14] Bulut et al., on the other hand, found deep surgical site infections in 33% of patients who underwent fasciotomy and believed that to broad the indication for fasciotomy increases the mortality.[15]

20 (46.5%) of 43 patients underwent surgical intervention and fasciotomy was performed in 7 (16.5%). This rate was found to be very low compared to the study by Sever et al. which reported that 50.5% of patients underwent fasciotomy in 639 patients and similar to the study by Oda et al. which reported that 13.1% of patients underwent fasciotomy in 372 patients.[16,17]

As in many studies, Michaelson recommends the initiation of fluid replacement under rubble to prevent acute kidney injury and crush syndrome.[6] Early and extensive fluid replacement was also shown to be effective in the Roodbar, Marmara and Kobe earthquake studies.[11,16,18] Patients receiving appropriate fluid therapy had less prolonged acute kidney injury and less requirement for hemodialysis.[7]

There was no significant difference between the amount of fluid given in the first 24 hours, the duration of hospitalization, time to reach the CK reference range and hemodialysis treatment. This was attributed to fluid replacement before hospitalization. Our center was far from the earthquake zone and it took a long time to transfer the patients. We think that fluid replacement during this period, that is, during the time the patients were under rubble and during their transfer to our center, was adequate. We believe that after adequate hydration is performed under the rubble and immediately afterwards and the patient is rendered normovolemic, it is not beneficial to give high amounts of fluid in the follow-up.

In our study, a statistically significant difference was found between the amount of fluid taken in the first 24 hours and urine output. This difference is thought to be a result of more controlled fluid administration in patients with low urine output in the first 24 hours.

Similar to the study of Sever et al., urine volume was lower and BUN, creatinine, phosphorus, LDH, potassium, CK levels were higher in patients on hemodialysis.[13] Unlike the study of Sever et al., the correlation between platelets, albumin, WBC and hemodialysis was not found in our study.[13]

In the Marmara earthquake and Taiwan earthquake it was suggested that there was a correlation between high CK levels at admission and hemodialysis and that it determined the need for hemodialysis.[8,19] The finding of CK levels above 5000 U/L in total of 6 patients (100%) who underwent hemodialysis supports this study.

As in the study by Zhang et al., lower serum sodium levels were found in patients on hemodialysis.[20] It is thought that sodium levels on admission may be used to predict the prognosis of crush syndrome.

Although hyponatremia has many causes, hypotonic hyponatremia is the most common type and is caused by non-osmotic secretion of vasopressin. Especially severe pain and fear experienced by patients trapped under rubble stimulate the secretion of vasopressin. Disruption of the functional integrity of the muscles and fluid losses into the interstitial space cause a decline in intravascular volume and consequently stimulate the secretion of vasopressin.[2,20] Westermann et al. reported that vasopressin was significantly elevated in patients with multiple injuries.[21]

The duration of hospitalization and the time to reach the CK reference range were found to be longer in patients with lower sodium levels on admission. Similar to the study of Zhang et al., low sodium levels are thought to be associated with poor prognosis.[20] In our study, more than half of the patients were hospitalized for more than 21 days. No study was found in the literature regarding the duration of hospitalization in crush syndrome. Patients with lower sodium and hemoglobin levels on admission had longer hospitalization. Anemia and hyponatremia are thought to be effective on the prognosis of the disease.

Decline of CK to the reference range is a signal that rhabdomyolysis is not persisting. There was no significant difference between patients who underwent hemodialysis and those who did not. The association of fasciotomy with the time to reach the reference range of CK is thought to be a result of more severe muscle damage in patients who underwent fasciotomy. There was a positive correlation with BUN, ALT, AST, CK, LDH, WBC, potassium and a negative correlation with sodium and calcium at admission. The correlation between the time to reach the CK reference range and the duration of hospitalization suggests that evaluation of these parameters during hospitalization may shorten the hospitalization period of patients and prevent complications that may be encountered due to prolonged hospitalization.

Our institution was distant from the earthquake zone and therefore the transfer of the patients required a long time. We believe that the fluid replacement therapy started under the

collapse was successfully continued during the transfer. A great deal of progress had already been recorded in this sense until the patients arrived at our center. After the earthquakes, many patients had been transferred to different provinces, especially closer to the earthquake region. The limitations of our study include the inability to work with a larger number of patients due to the low number of patients presenting to our center and the limited assessment of the registration and effectiveness of patients' initial fluid resuscitation treatments during the debris and transfer phases.

Conclusion

Our study revealed that patients with high CK levels required more surgical intervention and hemodialysis. In addition, hospital stay was prolonged in these patients. In crush syndrome, which is always a potential health problem for our country, which is located in the earthquake zone, the time and practices from the rapid detection of patients and safe vascular line placement under the collapse in coordination with search and rescue teams to transfer and close follow-up and treatment in the hospital are of crucial importance.

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CMJ,2024; 46(1): 74-77
DOI: 10.7197/cmj.1446187

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Our Clinic's Experience with Laser Hemorrhoidoplasty

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Research Article

History

Received: 03/03/2024
Accepted: 23/03/2024

ABSTRACT

Objective: We aim to present the outcomes of the Laser Hemorrhoidoplasty (LHP) procedure performed in our clinic.

Methods: In this retrospective study, we analyzed the outcomes of LHP performed on 112 patients in our clinic over a 24-month period. Patients were scheduled for follow-up visits at three weeks post-surgery, followed by subsequent follow-ups at three and six-month intervals.

Results: Of the 112 patients, 73 (65.17%) were male, and 39 (34.82%) were female. The mean age was 52.6 years (range: 20-65). The mean operation duration was 18.3 minutes (range: 12-25). Seventy patients were classified as grade 2, while 42 patients were classified as grade 3. The mean hospital stay was 1.16 days. While 5 of 70 patients with Grade 2 hemorrhoids could not be followed up after surgery, 24 were followed for 6 months and 41 for 1 year. One (1.42%) patient who attended the 1-year follow-up showed recurrence. Four patients (9.52%) showed recurrence. One patient with grade 3 hemorrhoids experienced postoperative bleeding lasting one week, requiring erythrocyte suspension transfusion. Another patient with grade 3 hemorrhoids developed a hematoma, which resolved with conservative treatment. Eight patients (7.14%) with grade 3 hemorrhoids developed postoperative edema, all of whom improved with conservative treatment. Pain, evaluated by the Visual Analog Scale, was measured as 2.03 on the first postoperative day and 1.49 on the second postoperative day.

Conclusion: LH treatment has been found to be a successful alternative treatment option for Grade 2 and Grade 3 diseases. It is emphasized that patient selection is crucial in LH treatment.

Keywords: Minimally invasive surgery, Hemorrhoid, Laser hemorrhoidoplasty

Lazer Hemoroidopeksi Klinik Deneyimimiz

Araştırma Makalesi

Süreç

Geliş: 03/03/2024
Kabul: 23/03/2024

ÖZET

Amaç: Kliniğimizde uygulanan Lazer Hemoroidoplasti (LHP) işleminin sonuçlarını sunmayı amaçladık

Yöntem: Bu retrospektif çalışmada, kliniğimizde 24 aylık bir dönemde yapılan LHP'nin sonuçlarını analiz ettik. Hastalar, ameliyat sonrası üç haftalık takip ziyaretleri planlandı, ardından üç ve altı aylık aralıklarla takip edildi.

Bulgular: 112 hastanın 73'ü (%65.17) erkek, 39'u (%34.82) kadındı. Ortalama yaş 52.6 idi (aralık: 20-65). Ortalama operasyon süresi 18.3 dakika idi (aralık: 12-25). Yetmiş hasta grade 2 olarak sınıflandırılırken, 42 hasta grade 3 olarak sınıflandırıldı. Ortalama hastanede kalış süresi 1.16 gün idi. Grade 2 hemoroidli 70 hastanın 5'i takipten çıkarıldı, 24'ü 6 ay ve 41'i 1 yıl boyunca takip edildi. Bir (1.42%) hasta 1 yıl sonundaki takipte nüks gösterdi. Dört hasta (%9.52) nüks gösterdi. Grade 3 hemoroidli bir hasta, bir hafta süren postoperatif kanama yaşadı ve eritrosit süspansiyonu transfüzyon ihtiyacı oldu. Grade 3 hemoroidli bir başka hasta, konservatif tedavi ile çözülen bir hematom geliştirdi. Grade 3 hemoroidli sekiz hastada (%7.14) postoperatif ödem gelişti, hepsi konservatif tedavi ile iyileşti. Görsel Analog Skala (VAS) kullanılarak ölçülen ağrı değerleri, birinci postoperatif günün 2.03, ikinci postoperatif günün ise 1.49 olarak ölçüldü.

Sonuç: LH tedavisi, Grade 2 ve Grade 3 hastalıklar için başarılı bir alternatif tedavi seçeneği olduğu düşünülmektedir ve LH tedavisinde hasta seçiminin kritik önem taşıdığı vurgulanmaktadır.

Anahtar Kelimeler: Minimal invazif cerrahi, Hemoroid, Lazer hemoroidoplasti

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How to Cite: Genç ÇH, Coşkun H, Demirtaş Y, Soylu S, Kurt A. Our Clinic's Experience with Laser Hemorrhoidoplasty. Cumhuriyet Medical Journal. 2024;46(1):74-77

Introduction

In today's surgical landscape, as with all surgical procedures, minimally invasive techniques have gained importance in the management of benign anorectal diseases. Due to high postoperative pain, high recurrence rates, and life-threatening complications such as bleeding and infection associated with traditional surgeries for benign anal conditions, there is ongoing exploration of new techniques. The incidence of symptomatic hemorrhoids is around 4%. It is a common health problem encountered in every society.[1,2] While conservative or medical treatment is the first-line approach in the management of early-stage hemorrhoids, surgical procedures may be necessary in case of treatment failure. Numerous surgical treatment options for hemorrhoids have been described, but none have been universally accepted as the gold standard.

Laser therapy is commonly used in surgery for conditions such as liver cancer, prostate cancer, and gynecological conditions.[3,4] Laser Hemorrhoidoplasty (LHP) is one of the minimally invasive surgical options for hemorrhoids, aiming to reduce and eliminate vascularity in the target hemorrhoid using a "laser beam." In recent years, Laser Hemorrhoidoplasty (LH) has been utilized as a novel treatment option. Initially described by Safli,[5] and Plapher,[6] this method has shown early postoperative benefits compared to other surgical methods.[7-10] Two randomized controlled trials reported less postoperative pain, quicker return to daily activities, and similar recurrence rates over a one-year follow-up period.[11,12]

Laser Hemorrhoidoplasty in our clinic has been performed only in patients with grade 2-3 hemorrhoids who do not have complaints such as thrombosis and active bleeding. In this report, we aim to present the outcomes of this procedure performed in our clinic and compare them with the literature.

Materials and Methods

This study was approved by the ethics committee of Sivas Cumhuriyet University Faculty of Medicine with decision number 2024-02/70.During the 24 months from September 2020 to December 2022, medical records of 112 patients who underwent LH for grade 2-3 hemorrhoidal disease at our clinic were retrospectively reviewed. Demographic characteristics, duration of follow-up, grades of hemorrhoids, complications, operative and hospital stay durations, pain scores, and recurrence data were recorded.

Surgical technique

A All patients underwent LH performed by a single surgeon with prior experience in LH. Procedures were conducted under general anesthesia. The neoV1470 system (G.N.S neo-Laser Ltd., Israel), equipped with a 1470 nm laser probe, was utilized. After grasping the enlarged hemorrhoid with a hemostat, the tip of the laser probe was inserted into the hemorrhoid pad, and the probe was positioned submucosally, reaching the apex of the hemorrhoid pad for the initial shot, followed by 4-6 shots around and into the pad. Manual pressure was applied to the pad after the removal of the laser probe. In cases of persistent bleeding, 3-0 Vicryl sutures were placed at the base of the hemorrhoid. Ice was applied to the anal canal with a sterile glove to reduce postoperative bleeding risk. Pressure dressings were applied postoperatively to minimize bleeding. At the end of the operation, a pudendal block was administered using 10 cc of bupivacaine. Post-operative analgesia was provided for 14 days with a non-steroidal anti-inflammatory drug (Ibuprofen, 400 mg twice Daily)

Follow-up

Patients were scheduled for follow-up visits at three weeks post-surgery, followed by subsequent follow-ups at three and six-month intervals. The outcomes of the patients were reported as complete resolution of all symptoms or partial improvement.

Results

Of the 112 patients, 73 (65.17%) were male, and 39 (34.82%) were female. The mean age was 52.6 years (range: 20-65). The mean operation duration was 18.3 minutes (range: 12-25). Seventy patients were classified as grade 2, while 42 patients were classified as grade 3. The mean hospital stay was 1.16 days. Among the 70 patients with grade 2 hemorrhoids, 5 were lost to follow-up, while 24 were followed up at 6 months and 41 at 1 year. One (1.42%) patient who attended the 1-year follow-up showed recurrence. Among the 42 patients with grade 3 hemorrhoids, 3 were lost to follow-up, while 13 were followed up at 6 months and 26 at 1 year. Four patients (9.52%) showed recurrence, with 1 at the 6-month follow-up and 3 at the 1-year follow-up. One patient with grade 3 hemorrhoids experienced postoperative bleeding lasting one week, requiring erythrocyte suspension replacement. Another patient with grade 3 hemorrhoids developed a hematoma, which resolved with conservative treatment. Eight patients (7.14%) with grade 3 hemorrhoids developed postoperative edema, all of whom improved with conservative treatment. Pain, evaluated using the Visual Analog Scale, was measured as 2.03 on the first postoperative day and 1.49 on the second postoperative day.

Discussion

When all patients undergoing LH were evaluated, the most significant advantages consistent with the literature were found to be reduced postoperative pain levels and shorter hospital stays. Additionally, it was observed that early complications such as bleeding, urinary retention, and infection were very rare, except for edema in the perianal area, which could be resolved with conservative treatment.

The first significant study evaluating the efficacy of LH was published in 2007, reporting a success rate of 88% in post-procedural follow-up.[13] Subsequent studies have reported similar success rates.[14-16]

In LH treatment, the laser probe is inserted into the submucosal layer of the hemorrhoid pad, emitting the laser beam for approximately 2 seconds to induce shrinkage of the hemorrhoid tissue. Tissue damage to surrounding areas is

limited to only 2 mm. After the hemorrhoid tissue shrinks, it is tightened with ice applied after the probe is removed.[17,18] In contrast, the classic Milligan Morgan (MM) operation may take more time for the surgeon to identify and preserve the sphincter muscles to protect normal anoderm and control bleeding.[19,20] With MM, the hemorrhoid pad, along with the overlying mucosa, is excised, resulting in a much larger wound size. As the wound size increases, it becomes more challenging to control bleeding, and postoperative pain is likely to be more severe, proportional to the size of the excised tissue.[21,22] We believe that one of the main reasons for the low VAS scores in the first 24 hours postoperatively in patients undergoing LH is this factor. LH specifically targets only the submucosal layer of the hemorrhoid pads, preserving muscles and nerve bundles, thus believed to be associated with a lower risk of urinary retention. None of our patients experienced urinary retention. It is believed that all these advantages of LHP, by shortening hospital stays, enable patients to return to their daily activities earlier.[15]

In hemorrhoid surgery, it is essential to avoid excessive damage to the normal anoderm and to preserve the sphincters.[23] One of the most important late complications seen in open surgery is the risk of anal stenosis. The more surgical damage is created, the more fibrous scar tissue will form. The risk of anal stenosis is lower in LH procedures because there is no tissue removal, sphincters are well preserved, and the wound is very small. We believe that the main reason for the low postoperative pain, absence of anal spasm, and minimal risk of late stenosis in the postoperative period is minimal surgical damage. In this group, patients had very little postoperative pain and were not encountered with anal stenosis during their follow-up. Anal incontinence was not observed in any patient.

When evaluated in terms of recurrence, Lie H et al.[24] stated in their study that there was no significant difference in recurrence between LH and classic hemorrhoid surgery. In our study group, a recurrence rate of 21.4% was determined, consistent with the literature. It was concluded that the size of the hemorrhoid pad and the stage of hemorrhoidal disease were the most significant factors determining recurrence.

In conclusion, LH treatment is a successful alternative treatment option for Grade 2 and Grade 3 diseases. It is emphasized that patient selection is crucial in LH treatment. Postoperative bleeding, edema, and possible late recurrences are more common when LH is performed in advanced-stage hemorrhoids. We think that LH treatment should not be preferred for complicated hemorrhoid patients and Grade 4 diseases.

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CMJ,2024; 46(1): 78-83
DOI: 10.7197/cmj.1409049

Cumhuriyet Medical Journal

| cmj.cumhuriyet.edu.tr | Founded: 2004 Available online, ISSN:1305-0028 Publisher: Sivas Cumhuriyet Üniversitesi

Anterior One- and Two-Level Cervical Corpectomy and Fusion for Cervical Spondylotic Myelopathy: A Retrospective Study

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Research Article

History

Received: 25/12/2024
Accepted: 26/03/2024

ABSTRACT

Introduction: Anterior cervical corpectomy is a frequently employed surgical procedure used to decompress the spinal cord in the surgical treatment of cervical spondylotic myelopathy.This study investigated the clinical and radiologic outcomes and complications of one- and two-level anterior cervical corpectomy.

Methods: A retrospective evaluation was conducted on patients with cervical spondylotic myelopathy who underwent one- and two-level anterior cervical corpectomy between 2006 and 2022. The primary outcomes were clinically assessed using the visual analog scale to measure neck pain and radiologically based on the sagittal C2–C7 and T1 slope angles. Further, the results were evaluated in terms of complications and fusion.

Results: The one-level and two-level corpectomy groups comprised 16 and 9 patients, respectively, resulting in a total of 25 patients who underwent anterior cervical corpectomy. The postoperative visual analog scale scores significantly decreased in both groups compared with that of baseline ($p = 0.001$; $p < 0.01$ and $p = 0.007$; $p < 0.01$). Similarly, the postoperative T1 slope angle showed a significant decrease compared with that of baseline in both groups ($p = 0.001$; $p < 0.01$ and $p = 0.007$; $p < 0.01$), while the postoperative C2–C7 angle significantly increased in both groups compared with that of baseline ($p = 0.001$; $p < 0.01$ and $p = 0.007$; $p < 0.01$). However, no significant differences were observed in terms of preoperative and postoperative visual analog scale scores, T1 slope angle, C2–C7 angles, and changes from baseline between the groups ($p > 0.05$), ($p = 0.637$; $p > 0.05$), ($p = 0.169$; $p > 0.05$), and ($p > 0.05$), ($p = 0.452$; $p > 0.05$). The operation duration for patients in the two-level group was significantly longer than that in the one-level group ($p = 0.007$; $p < 0.01$).

Conclusion: The study findings indicated no significant clinical or radiological differences between cases undergoing one-level and two-level anterior corpectomy, except for the differences observed in operation duration. While anterior cervical corpectomy presents surgical challenges and carries a relatively higher risk of complications, meticulous surgical techniques can yield satisfactory outcomes, particularly in the context of one- and two-level anterior corpectomy.

Keywords: Retrospective studies, Cervical vertebrae, Myelopathy, Kyphosis, Surgical decompression.

Servikal Spondilotik Miyelopatide Ön Bir ve İki Seviyeli Servikal Korpektomi ve Füzyon: Retrospektif Bir Çalışma

Araştırma Makalesi

Süreç

Geliş: 25/12/2024
Kabul: 26/03/2024

ÖZET

Amaç: Anterior servikal korpektomi, servikal myelopatik spondilopatinin cerrahi tedavisinde spinal kordun dekompresyonunu sağlamak için kullanılan yaygın bir omurga cerrahisi prosedürüdür. Bu çalışmanın amacı bir ve iki seviye anterior servikal korpektominin klinik,radyolojik sonuçlarını ve komplikasyonlarını araştırmaktır.

Yöntem: 2006 -2022 yılları arasında bir ve iki seviyeli anterior servikal korpektomi cerrahisi uygulanan servikal spondilotik myelopati hastaları rekrospektif olarak değerlendirmeye alınmıştır. Birincil olarak vakaların sonuçları klinik olarak vizüel analog skala (VAS) ile ölçülen boyun ağrısı ile, radyolojik olarak sagittal c2-c7 ve T1 slope açısı üzerinden değerlendirilmiştir. İkincil olarak sonuçlar komplikasyonlar ve füzyon açısından değerlendirilmiştir.

Bulgular: Bir seviyeli korpektomi grubunda 16, iki seviyeli korpektomi grubunda 9 hasta yer aldı ve toplam 25 hastaya anterior servikal korpektomi uygulanmıştır. Her iki grubun postoperatif vas değerleri preoperatife göre anlamlı derecede azalmıştır. (p=0,001; p<0,01) ve (p=0,007; p<0,01) Her iki grubun preoperatife göre t1 slop açısı postoperatif anlamlı derecede azalmıştır. (p=0,001; p<0,01), (p=0,007; p<0,01) Yine her iki grubun preoperatife göre postoperatif c2-c7 açısı anlamlı derecede artmıştır. (p=0,001; p<0,01), (p=0,007; p<0,01) Ancak gruplar arasında preoperatif ve postoperatif vas, t1 slop açı ,c2-c7 açı değerleri ve değişimleri arasında fark bulunmadı. (p>0,05), (p=0,637; p>0,05) ve (p>0,05), (p=0,169; p>0,05) ve (p>0,05),(p=0,452; p>0,05) İki seviye grubundaki olguların ameliyat süresi, bir seviye grubundan istatistiksel olarak anlamlı düzeyde uzun saptanmıştır (p=0,007; p<0,01).

Sonuç: Elde edilen bulgulara göre bir seviye ve iki seviyeli anterior korpektomi vakalarının arasında klinik ve radyolojik olarak ameliyat süresi dışında fark tesbit edilmedi. Anterior servikal korpektomi zorlu bir ameliyat tekniği olması ve nisbeten fazla komplikasyonları olmasına rağmen özenli bir cerrahi uygulama ile özellikle bir ve iki seviye anterior korpektomide tatminkar sonuçlar alınabilir.

Anahtar Kelimeler: Retrospektif çalışmalar, Servikal vertebralar, Miyelopati, Kifoz, Cerrahi dekompresyon..

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How to Cite: Doğu H. Anterior One- and Two-Level Cervical Corpectomy and Fusion for Cervical Spondylotic Myelopathy: A Retrospective Study. Cumhuriyet Medical Journal. 2024;46(1):78-83

Introduction

Cervical spondylotic myelopathy is characterized by a gradual and insidious onset of symptoms and is more prevalent among the elderly. Early diagnosis and treatment are crucial; advanced cases often necessitate surgical intervention. If left untreated, the condition can result in progressive neurological deficits and lead to permanent sequelae.[1] Because of the degenerative nature of the underlying condition, it often affects multiple segments of the cervical spine, leading to frequent involvement across multiple levels.

In cervical spondylotic myelopathy, the compression typically occurs anteriorly, for which anterior cervical corpectomy and fusion have been the long-established surgical procedures.[2] Anterior cervical corpectomy offers a safe and effective surgical approach for addressing traumatic, neoplastic, and infective diseases affecting the cervical region, particularly in cases of cervical spondylotic myelopathy.[3] Further, there are alternative surgical methods such as posterior decompression and fusion or combined interventions. The superiority between methods or their preferred application in specific cases is debated.

Anterior cervical corpectomy offers several advantages, including more effective decompression, particularly in cases of anterior compression. It also facilitates the restoration of cervical lordosis and has a high fusion success rate.[4] However, it is a more invasive technique compared with posterior approaches, primarily because of the presence of the trachea, esophagus, and vascular structures within the operative field. In contrast, posterior decompression, despite being a less invasive surgery, is associated with drawbacks such as the potential for C5 root palsy or the development of progressive cervical kyphosis.[5,6] The results of low-level anterior cervical corpectomies are encouraging; multilevel anterior cervical corpectomies become more invasive and challenging, and the likelihood of complications increases.[7]

We conducted a retrospective analysis of patients with cervical spondylotic myelopathy who underwent one or two-level anterior cervical corpectomy surgeries in this study. The assessment focused on evaluating clinical and radiological results, early and long-term outcomes, as well as complications.

Materials and methods

Patients

The study was approved by the local ethics committee (reference number: E-22686390-050.99-36167). We analyzed patients who underwent one- and two-level anterior cervical corpectomy with the diagnosis of cervical spondylotic myelopathy in our center between 2006 and 2022 retrospectively. Preoperative and postoperative clinical assessments of the patients were conducted using the visual analog scale (VAS). All patients underwent preoperative radiological assessments, including anteroposterior and lateral neutral cervical radiography, dynamic cervical radiography, cervical computed tomography, and cervical magnetic resonance imaging (MRI) (Figure 1). The inclusion criteria comprised persistent neck and radicular pain, neurological deficits, and radiological evidence indicating stenosis caused by anterior compression. All patients underwent anterior cervical corpectomy, followed by stabilization achieved through the use of an anterior plate and expandable cage. Patients undergoing posterior or combined interventions were excluded from the study. Patients with malignancy, trauma, or infection were also excluded from the study. The surgical procedures were conducted at a single center by a single surgeon (H.D.). Age, gender, and neurologic status of the patients were recorded. All patients underwent cervical radiography at 1 month, 6 months, and 1 year. The T1 slope and C2–C7 lordosis angle values were used in the evaluation. The cervical lordosis angle is the angle between the inferior end plate of the C2 vertebra and the inferior end plate of the C7 vertebra. The T1 slope was defined as the angle between the superior end plate of the T1 vertebra and the horizontal line.[8]

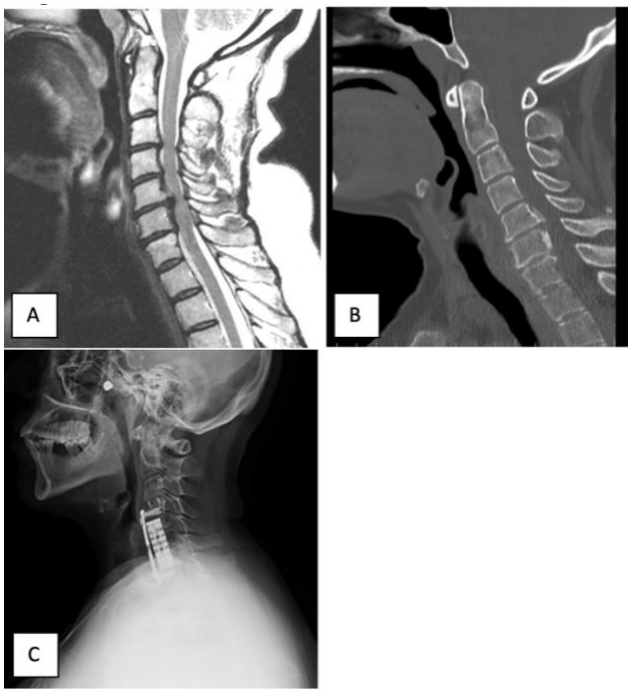

Figure-1. Imaging findings in a patient with two-level cervical spondylotic myelopathy. A. Preoperative sagittal T2-weighted images show severe stenosis at the C5–C6 level. B. Computed tomography scan of the cervical vertebra in the sagittal plane without contrast enhancement in the preoperative phase shows a calcified herniated disc in the bone window. C. Postoperative lateral neutral cervical radiograph showing C5 and C6 corpectomy cage, anterior cervical plate, and peek cage at the C3–C4 space.

Surgical technique

Standard cervical anterior approach was used, and a vertical incision was made. The trachea and esophagus were medially retracted, and the neurovascular bundle was laterally retracted. The retractor was intermittently loosened during the operation to protect the laryngeal nerve. Anterior discectomy was conducted both above and below the corpectomy level. The bone fragments retrieved during corpectomy were preserved for use during the fusion procedure. Corpectomy was conducted using a high-speed

drill. The height of the expandable cages was customized to match the corpectomy site. Autograft was employed for the fusion procedure, and it was fixed with an anterior plate. Fluoroscopy was used to check the instrumentation, and a drain was inserted. No blood transfusions were administered to any patient.

Postoperative anteroposterior and lateral cervical radiographs were taken on day 1 for all patients. After the surgery, patients were advised to use cervical collars for 6 weeks. Follow-up clinical examinations were conducted on postoperative days 7 and 20, as well as at 3 months, 6 months, and 1 year. Dynamic cervical radiography was performed for fusion control. Mobility exceeding 2° on flexion-extension radiographs, the existence of a radiolucent area between the end plate and the graft, or the absence of bone trabeculae were considered to indicate pseudoarthrosis.

Statistical analysis

During the evaluation of the study's findings, statistical analysis was conducted using the IBM SPSS version 27. During the study data analysis, quantitative variables were represented using measures such as mean, standard deviation, median, minimum, and maximum values. Qualitative variables were presented as descriptive statistics, including frequency and percentage. Shapiro–Wilk test and box plots were used to evaluate the normality of the data.

Mann–Whitney U test was used to compare non-normally distributed quantitative variables between the two groups. Wilcoxon signed-rank test was used to compare non-normally distributed variables between the two follow-up measurements. Fisher's exact test was used to compare qualitative data.

The results were assessed within a 95% confidence interval, and the significance was determined at $p < 0.05$.

Results

The study was conducted at Hospital with a total of 25 patients, comprising 19 (76%) women and 6 (24%) men. The mean age of the participating patients was 62.28 ± 7.11 years (range: 50–73 years) (Table 1). Sixteen patients underwent one-level anterior cervical corpectomy, with the most frequently involved level being C6. Nine patients underwent two-level anterior cervical corpectomy, with the most frequently involved level being C5–C6.

There was no difference between the groups in terms of age and gender ($p > 0.05$), but the operative time in the two-level group was significantly longer than that in the one-level group ($p = 0.007$).

All patients had cervical spondylotic myelopathy, with 16 individuals (64%) exhibiting myelomalacia findings on cervical MRI. The most common complaint was neck and radicular pain (96%), followed by sensory changes (76%) and muscle weakness (64%). None of the patients experienced neurologic deterioration, and no mortality occurred. Two patients (after 3 and 5 years) died of other causes. The mean length of hospital stay was 2.28 (2–7) days.

The mean duration of follow-up after surgery was 2.5 years (1–9 years). At the 1-year follow-up radiography, fusion findings were observed in 96% of the patients. Two patients underwent anterior discectomy and cage application in a different segment, alongside the corpectomy procedure.

Based on preoperative and postoperative VAS scores, both groups benefited from surgery. The decrease of 2.94 ± 1.53 points in the postoperative VAS score of the patients in the one-level group compared with baseline and the decrease of 3.11 ± 1.45 points in the postoperative VAS scores of the patients in the two-level group compared with baseline were statistically significant ($p = 0.001$ and $p = 0.007$, respectively). Preoperative and postoperative VAS scores ($p > 0.05$) and the change from baseline ($p = 0.637$) did not show significant differences between the groups ($p > 0.05$) (Table 2).

Preoperative and postoperative T1 slope angles did not show significant differences between the groups ($p > 0.05$). The decrease in postoperative T1 slope angles from baseline was 1.44° ± 1.09° in the one-level group and 2.56° ± 2.07° in the two-level group, and the differences were statistically significant ($p = 0.001$ and $p = 0.007$, respectively). In the comparison between the groups, the difference in the postoperative T1 slope angles and the change from baseline was not statistically significant ($p = 0.169$).

Both groups experienced postoperative gain in lordosis angle. The increase in postoperative C2–C7 values from baseline was 3.31° ± 2.36° in the one-level group and 2.68° ± 2.41° in the two-level group, and the differences were statistically significant ($p = 0.001$ and $p = 0.007$, respectively). Preoperative and postoperative C2–C7 angle values and the change from baseline did not show significant differences between the groups ($p = 0.452$).

In the one-level group, transient dysphagia (1 patient), transient dysphonia (1 patient), and a simple superficial infection (1 patient) were detected. The superficial infection (subcutaneous abscess) was treated with a 10-day course of antibiotic therapy. In the two-level group, one patient experienced intraoperative dural rupture due to adhesion. The dural rupture was repaired using primary sutures through the corpectomy site. The postoperative follow-up did not show any problems related to cerebrospinal fluid. In another patient within the two-level group, pseudoarthrosis was noted; however, reoperation was not deemed necessary because of the absence of clinical complaints. Additionally, neither cage slippage nor plate dislocation was observed in any patient from both groups during both early and late periods.

Table-1. Comparison of descriptive characteristics by groups

	Cervical corpectomy group		p
	One-level (n = 16)	Two-level (n = 9)	
Gender			
Women	13 (81.3)	6 (66.7)	†0.630
Men	3 (18.8)	3 (33.3)	
Age (years)			
Mean ± SD	63.19 ± 7.00	60.67 ± 7.43	‡0.329
Median (minimum-maximum)	63.5 (49.9–73.4)	56.9 (51.7–71.9)	
Duration of surgery (min)			
Mean ± SD	186.25 ± 24.12	238.89 ± 56.22	‡0.007**
Median (minimum-maximum)	185 (155–220)	220 (180–350)	

Fisher's exact test; ‡ Mann–Whitney U test; ** p < 0.01. SD, standard deviation.

Table-2. Comparison of visual analog scale scores, T1 slope, and C2–C7 angle measurements between the groups.

		Cervical corpectomy group		†p
		One-level (n = 16)	Two-level (n = 9)	
VAS Score				
Preoperative phase	Mean ± SD	5.69 ± 1.14	6.00 ± 1.22	0.522
	Median (minimum-maximum)	5.5 (4–8)	6 (4–8)	
Postoperative phase	Mean ± SD	2.75 ± 0.77	2.89 ± 0.78	0.677
	Median (minimum-maximum)	3 (2–4)	3 (2–4)	
	‡p	0.001**	0.007**	
Change Δ	Mean ± SD	−2.94 ± 1.53	−3.11 ± 1.45	0.637
T1 Slope Angle				
Preoperative phase	Mean ± SD	21.06 ± 2.46	21.11 ± 2.67	0.978
	Median (minimum-maximum)	21 (17–25)	21 (17–25)	
Postoperative phase	Mean ± SD	19.63 ± 2.22	18.56 ± 2.19	0.301
	Median (minimum-maximum)	20 (16–24)	19 (16–22)	
	‡p	0.001**	0.007**	
Change Δ	Mean ± SD	−1.44 ± 1.09	−2.56 ± 2.07	0.169
C2–C7 Angle				
Preoperative phase	Mean ± SD	5.75 ± 3.42	5.9 ± 2.46	0.718
	Median (minimum-maximum)	5 (1–12)	5 (3.1–11)	
Postoperative phase	Mean ± SD	9.06 ± 3.43	8.58 ± 2.65	1.000
	Median (minimum-maximum)	8 (5–17)	8 (5–13)	
	‡p	0.001**	0.007**	
Change Δ	Mean ± SD	3.31 ± 2.36	2.68 ± 2.41	0.452

VAS, visual analog scale; †Mann–Whitney U test; ‡Wilcoxon signed-rank test; **, p < 0.01.

Discussion

In this study, we investigated the early and late outcomes in cases of cervical spondylotic myelopathy treated surgically with one- or two-level anterior cervical corpectomy. Our study findings indicate that conducting anterior cervical corpectomy along with cage plate application proved to be an effective and safe method for treating cervical spondylotic myelopathy surgically.

An effective anterior cervical corpectomy should achieve fusion, restore cervical alignment as close to neutral as possible, and significantly enhance the patient's quality of life. Simultaneously, it should have the lowest incidence of early or late complications. Previous studies have reported a high rate of fusion with anterior cervical corpectomy. Kotil and Tari[1] reported a series of 21 patients undergoing two-level corpectomy. They achieved fusion in all cases (100%) using a graft harvested from the iliac wing. Similarly, Tome-Bermejo et al.[9] reported a series of 56 cases undergoing one- or two-level corpectomy and a 98% fusion rate. However, Bayerl et al.[10] compared anterior intervention with combined anterior–posterior intervention in a study involving 21

patients who underwent corpectomy. They reported a 33% rate of instrument failure with anterior intervention.

A robust instrumentation is necessary to ensure an effective fusion. Instrument failure was not observed in any case in our study. Fusion was achieved in 96% of cases; revision surgery was not required.

In addition to fusion, cervical alignment is another crucial factor influencing outcomes following anterior cervical corpectomy. Disturbance in cervical alignment negatively affects the comfort experienced in daily life. Kotil and Tari[1] reported a mean kyphosis improvement of 25.2° in all patients. Darry Lau et al.[11] reported a postoperative lordosis angle gain of 7.7° in a series of 35 cases undergoing cervical anterior corpectomy. In our series, the lordosis angle gain was 3.31° ± 2.36° in the one-level corpectomy group and 2.68° ± 2.41° in the two-level corpectomy group.

The necessity of posterior fusion due to the inability to achieve fusion after anterior corpectomy has been reported in many studies [3,10]. Tatter et al.[3] reported 119 cases undergoing anterior cervical corpectomies due to different pathologies. At a single level, a high fusion success rate was reported, while cases involving multiple levels required subsequent posterior fusion. However, in our study, which involved both one- and two-level anterior cervical corpectomies, no cases required posterior intervention or fusion.

Some authors have examined or compared cases undergoing one- and two-level anterior cervical corpectomies. Ozgen et al.[12] performed one-level anterior cervical corpectomy in 37 (51.4%) patients and two-level anterior cervical corpectomy in 35 (48.6%) patients. In their series of 72 cases, fusion was achieved at a rate of 92.9%, and the outcomes were satisfactory in 88% of the patients. Five patients experienced graft-related complications, and seven patients experienced plate-related complications. Similarly, Hartmann et al.[13] compared one- and two-level anterior cervical corpectomy cases in their series involving 45 cases. They identified a 22.9% (10 cases) rate of complications, which included six instrument-related complications and two cases of hematoma. Four patients had neurological deterioration. All complicated cases underwent revision surgery. However, their report indicated no correlation between the number of corpectomy levels and instrument failure.

Tome-Bermejo et al.[10] presented a series of 56 cases undergoing one- or two-level anterior cervical corpectomy. They achieved fusion in 98% of their patients and reported good outcomes. One patient experienced esophageal bleeding, while another patient experienced instrument dislocation requiring reoperation. Yu et al.[7] evaluated the results of two-, three-, and four-level anterior cervical corpectomy in a study of 248 cases. They reported that as the number of levels increased, blood loss, operation time, complications, Neck Disability Index score, and cervical range of motion were negatively affected. In our study, the operation time was significantly longer in the two-level corpectomy group than in the one-level group, but there was no difference between them in terms of VAS score and radiological outcomes.

Complications following cervical anterior corpectomy have been reported to range between 11% and 27% [11,12]. Some of these include vocal cord paralysis, dysphagia, tracheal and/or esophageal injury, cerebrospinal fluid fistula, and surgical site infections [4]. In our study, one patient experienced transient dysphagia, while another patient experienced dysphonia, both of which resolved within a few days. In addition, one patient experienced a dural rupture, which was repaired with primary suture and did not cause a cerebrospinal fluid fistula.

Limitations

Both groups in our study had a limited number of cases. There is a need for studies involving a larger number of patients. This study exclusively compared one- and two-level corpectomies. Future evaluations could expand to include comparisons with multilevel corpectomies. Moreover, our study was retrospective, conducted at a single center, and conducted by a single surgeon. In the future, multicenter prospective studies will allow us to obtain larger and more diverse data sets.

Conclusion

This study evaluated the long-term outcomes of patients undergoing one- or two-level corpectomy. Our findings indicated no significant clinical or radiological differences between one- and two-level anterior cervical corpectomy cases, except for the duration of surgery. Anterior cervical corpectomy presents a challenging surgical technique with a relatively high risk of complications. However, employing a meticulous surgical approach yields satisfactory outcomes, particularly in patients undergoing one- or two-level anterior cervical corpectomy.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest concerning this article's research, authorship, and publication.

Funding

The author received no financial support for this article's research, authorship, and publication

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