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İletişim/ *Contact*: Alanya Alaaddin Keykubat Üniversitesi Tıp Fakültesi Temel Tıp Bilimleri BinasıKestel Kampüsü, Alanya / Antalya. mail: actamedica@alanya.edu.tr Tel/Phone: +905056462411

EDİTÖRYAL DANIŞMA KURULU

TEMEL TIP BİLİMLERİ (Alfabetik sırayla, Güncelleme: 27.03.2022)

DAHİLİ TIP BİLİMLERİ (Alfabetik sırayla, Güncelleme: 27.03.2022)

Güven Yılmaz, Uzman Dr, cesus20@gmail.com
Sağlık Bilimleri Üniversitesi, Kartal Eğitim ve Araştırma Hastanesi, Hematoloji Kliniği, İstanbul/Türkiye

Hakan Gür, Prof.Dr. hakangur2001@gmail.com
Uludağ Üniversitesi, Tıp Fakültesi, Spor Hekimliği AD, Bursa/Türkiye

Hacer Erdem Tilki, Prof. Dr. hacererdem@gmail.com
Ondokuz Mayıs Üniversitesi, Tıp Fakültesi, Klinik Nörofizyoloji BD. Samsun/ Türkiye

Ersin Sayar, Dr. Öğr. Üyesi, ersin.sayar@alanya.edu.tr
ALKÜ, Tıp Fakültesi, Çocuk Sağlığı ve Hastalıkları/ Çocuk Gastroenteroloji BD. Alanya/Türkiye

İnci Meltem Atay, Doç.Dr. incimeltem@gmail.com
Süeyman Demirel Üniversitesi, Tıp Fakültesi, Psikiatri AD, Isparta /Türkiye

Murat Baykara, Dr.Öğr.Üyesi, mbaykara@hotmail.com Fırat Üniversitesi, Tıp Fakültesi, Radyoloji AD, Elazığ/Türkiye

Mustafa Öztürk, Prof.Dr. muozturk32@gmail.com
Karabük Üniversitesi, Tıp fakültesi, Halk Sağlığı AD, Karabük/Türkiye

Mustafa Adlı, Prof.Dr. madli@hotmail.com
Marmara Üniversitesi, Tıp Fakültesi, Radyasyon Onkolojisi AD. İstanbul/ Türkiye

Mustafa Sait Gönen, Prof.Dr. gonen.sait@gmail.com
İ.Ü. Cerrahpaşa Tıp Fakültesi ,İç Hastalıkları AD, Endokrinoloji ve Metabolizma BD, İstanbul/Türkiye

Neşe Demirtürk, Doç.Dr. nesed60@hotmail.com
Afyon Sağlık Bilimleri Üniversitesi, Tıp Fakültesi, Enfeksiyon Hastalıkları AD, Afyonkarahisar /Türkiye

Nilay Şahin, Doç.Dr. dincernilay@yahoo.com
Balıkesir Üniversitesi, Tıp Fakültesi, Fizik tedavi ve Rehabiliatasyon AD, Balıkesir /Türkiye

Tayfun Kara, Dr. Öğr. Üyesi, tayfun.kara@alanya.edu.tr
ALKÜ, Tıp Fakültesi, Çocuk ve Ergen Ruh Sağlığı ve Hastalıkları AD. Alanya/Türkiye

Süleyman Kutluhan, Prof.Dr. skutluhan@hotmail.com
Süeyman Demirel Üniversitesi, Tıp Fakültesi, Nöroloji AD, Isparta /Türkiye

Hatice Lakadamyalı, Prof.Dr. hatice.lakadamyali@alanya.edu.tr
Alanya Alaaddin Keykubat Üniversitesi, Tıp Fakültesi, Radyoloji AD. Alanya/Türkiye

CERRAHİ TIP BİLİMLERİ (Alfabetik sırayla, Güncelleme: 27.03.2022)

Adalet Demir, Prof.Dr. dradalet@hotmail.com
Özel Medical Park Bahçeşehir Hastanesi, Göğüs Cerrahisi Kliniği, İstanbul/Türkiye

Altuğ Tuncel, Prof.Dr. tuncelaltug@yahoo.com
Sağlık Bilimleri Üniversitesi, Ankara Numune Eğitim ve Araştırma Hastanesi, Üroloji Kliniği, Ankara/Türkiye

Atilla Sezgin, Prof.Dr. asezgin@baskent.edu.tr
Başkent Üniversitesi, Tıp Fakültesi, Kalp-Damar Cerrahisi AD, Çocuk Kalp Damar Cerrahisi BD. Ankara/Türkiye

Cemil Ertürk, Doç.Dr. erturkc@yahoo.com
SBU, İstanbul Kanuni Sultan Süleyman SUAM, Ortopedi ve Travmatoloji Kliniği , İstanbul, Türkiye

Fevzi Yılmaz, Doç.Dr. fevzi_yilmaz2002@yahoo.com
Sağlık Bilimleri Üniversitesi, Antalya Eğitim ve Araştırma Hastanesi, Acil Tıp Kliniği. Antalya/Türkiye

Hakan Kaya, Prof.Dr. drhakankaya2002@yahoo.com
Özel Isparta Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Isparta/Türkiye

Hasan Kamil Sucu, Doç.Dr. hksucu@gmail.com
İzmir Katip Çelebi Üniversitesi, Atatürk Eğitim ve Araştırma Hastanesi, Nöroşurji Kliniği, İzmir/Türkiye

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EDITORIAL

EDİTÖRYAL

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Acute Kidney Injury in Children

Çocuklarda Akut Böbrek Hasarı

Arife Uslu Gökceoğlu[1], Ahmet Aslan[2*]

1Medical School of Alanya Alaaddin Keykubat University, Department of Pediatric Nephrology Alanya/Antalya, Türkiye
2Medical School of Alanya Alaaddin Keykubat University, Department of Orthopedics and Traumatology, Alanya/Antalya, Türkiye

ABSTRACT

Acute kidney injury (AKI) is a clinical condition characterized by sudden deterioration in kidney functions, increase in blood urea nitrogen (BUN) and serum creatinine levels, hyperkalemia, metabolic acidosis and hypertension. When defining AKI, current guidelines that consist of criterias determined by serum creatinine level and urine output are used. There are three main causes of AKI; prerenal, renal and postrenal. Prerenal AKI is most common etiology in children. Clinical symptoms of AKI vary depending on etiology. When evaluating a child with AKI, it should be noted that an increase in creatinine typically occurs 48 hours after renal injury and is the result of events 2-3 days earlier. The prognosis of AKI varies depending on the etiology.

ABSTRACT

Keywords: child, acute kidney injury, serum creatinine, urine output

ÖZ

Akut böbrek hasarı (ABH), böbrek fonksiyonlarında ani bozulma, kan üre nitrojeni (BUN) ve serum kreatinin düzeyinde artış, hiperkalemi, metabolik asidoz ve hipertansiyon ile karakterize klinik bir durumdur. ABH tanımlanırken, serum kreatinin düzeyi ve idrar miktarına göre belirlenen kriterlerden oluşan güncel kılavuzlar kullanılmaktadır. ABH'nın üç ana nedeni vardır; prerenal, renal ve postrenal. Prerenal ABH, çocuklarda en sık görülen etyolojidir. ABH'nın klinik semptomları etiyolojiye göre farklılık gösterir. ABH'li bir çocuğu değerlendirirken, kreatinin düzeyindeki artışın tipik olarak böbrek hasarından 48 saat sonra meydana geldiği ve 2-3 gün önceki olayların sonucu olduğu unutulmamalıdır. ABH'nın prognozu etyolojiye göre değişiklik göstermektedir.

Anahtar kelimeler: çocuk, akut böbrek hasarı, serum kreatinin, idrar miktarı

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* Corresponding Author: Ahmet Aslan, MD, Medical School of Alanya Alaaddin Keykubat University, Department of Orthopedics and Traumatology, Alanya/Antalya, Türkiye. Phone: 05056462411 / mail: ahmet.aslan@alanya.edu.tr

ORCID: 0000-0001-5797-1287

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Acute kidney injury (AKI) is a clinical condition characterized by sudden deterioration in kidney functions, increase in blood urea nitrogen (BUN) and serum creatinine, hyperkalemia, metabolic acidosis and hypertension [1]. In the past, acute renal failure (ARF) was used and it has been called AKI since 2004 [2]. The development of AKI has been reported in 2-3% of hospitalized children and 8% of those in the neonatal intensive care unit [3].

When defining AKI, current guidelines such as RIFLE, pediatric RIFLE, Acute Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) are used [4-7, Table 1]. Early diagnosis and determining the clinical severity of AKI are important issues for prognosis. RIFLE criteria is a definition consisting of the initials of English words such as risk (R), injury (I), failure (F), loss (L) and end stage renal disease (E) and began to be used in 2004. Subsequently, the pediatric RIFLE criteria, which recommended the use of the same abbreviation in children, came into use. Pediatric RIFLE includes criteria determined based on serum creatinine and urine output. AKIN criterias and KDIGO criterias were published in 2007 and 2012 respectively. Both criterias evaluated AKI at three stages.

The etiology of AKI is evaluated under 3 main causes: prerenal, renal and postrenal causes. Prerenal causes are most commonly seen in

children. Dehydration and gastroenteritis are the most common causes of AKI [1]. Conditions such as extracellular fluid loss, systemic vasodilation, decreased renal blood flow, and increased resistance to flow are the causes of prerenal AKI. Conditions that cause tubular damage and glomerulonephritis are causes of renal AKI. Congenital or acquired conditions that impair urine flow are also considered as postrenal AKI [8]. Clinical findings differ according to etiology. For example; oliguria along with clinical signs of dehydration may be observed in a child with AKI secondary to gastroenteritis, one of the causes of prerenal AKI. Hypervolemia findings due to oliguria may be observed in a child with AKI secondary to glomerulonephritis due to renal causes, and anuria may be observed in a patient with AKI secondary to renal stone due to postrenal causes [1]. Although an infant presenting with vomiting and diarrhea for three days is more likely to have prerenal AKI with signs of dehydration, the diagnosis of hemolytic uremic syndrome (HUS) that is renal etiology of AKI should also be considered. If there is history of pharyngitis, periorbital edema, hypertension and macroscopic hematuria, renal AKI secondary to acute post-infectious glomerulonephritis should be considered as differential diagnoses. Acute tubular necrosis should be considered in patients with resistant hypotension or a history of nephrotoxic drug use. A male newborn with bilateral hydronephrosis on prenatal ultrasonography and a palpable bladder on physical examination should be evaluated for the posterior urethral valve. A detailed physical examination should be performed and the patient's volume status should be carefully evaluated. If AKI is accompanied by rash and arthritis, SLE (systemic lupus erythematosus) or IgA vasculitis should be considered. If there are palpable kidneys on physical examination, renal vein thrombosis, tumor, cystic diseases or urinary system obstruction should be considered in the differential diagnosis [3].

When evaluating a children with AKI, it should be noted that an increase in creatinine typically occurs 48 hours after renal injury and is the result of events 2-3 days before. For this reason, hypotension, hypoxia, sepsis, surgical intervention, contrast material and drug exposure should be questioned 48-72 hours before AKI is identified [8]. Serum creatinine is considered a late biomarker of AKI as that increases after AKI develops. Biomarkers such as Neutrophil gelatinase associated lipocalin (NGAL), Kidney injury molecule-1, and IL-18, which help to define AKI earlier, have been identified, but have not yet come into routine use [9]. Development of sensitive biomarkers to define AKI earlier is important to initiate treatment at the appropriate time [10]. In the diagnostic evaluation of AKI; urine examination, basic serum electrolyte levels, kidney function tests and urinary system imaging, especially ultrasonography, are the most important diagnostic tools [8].

Table1: Criterias Used in Defining Acute Kidney Injury In Children (ESRD: end stage renal disease, e GFR: estimated glomerular filtration rate, h: hour)

Criteria	Stage	Serum creatinine	Urine output
pRIFLE	Risk	eGFR decrease by 25%	< 0.5ml/kg/h for 8 h
	Injury	eGFR decrease by 50%	< 0.5ml/kg/h for 16 h
	Failure	eGFR decrease by 75%	< 0.3ml/kg/h for 24 h or anuria for 12 h
	Loss	Persistent failure > 4 weeks	
	ESRD	Persistent failure > 3 months	
AKIN	1	Increase in serum creatinine x 1,5-2 or increase in serum creatinine > 0.3mg/dl	<0.5ml/kg/h for 6h
	2	Increase in serum creatinine x 2-3	<0.5ml/kg/h for 12 h
	3	Increase in serum creatinine x 3 or serum creatinine >4 mg/dl (acute increase >0,5 mg/ dl) or Renal Replacement Treatment	<0.3ml/kg/h for 24h or anuria for 12 h
KDIGO	1	Increase in serum creatinine x 1,5-1,9 or increase in serum creatinine >0,3mg/dl within 48 h	<0.5 ml/kg/h for 6 h
	2	Increase in serum creatinine x 2-2,9	<0.5ml/kg/h for 12 h
	3	Increase in serum creatinine x 3 or serum creatinine ≥ 4mg/dl or renal replacement therapy	<0.3ml/kg/h for 24 h or anuria for 12h

The prognosis of AKI depends on the etiology of AKI. Children who develop AKI as a component of multisystem failure have a higher mortality rate than AKI that develops secondary to primary renal diseases such as HUS, rapidly progressive glomerulonephritis (RPGN) and acute interstitial nephritis (AIN). Recovery from AKI secondary to

primary renal disease varies depending on the underlying etiology. Nephrotoxic AKI and hypoxic/ischemic AKI usually result in recovery of normal renal function [10].

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ORCID and Author contribution: **A.U.G.(0000-0002-5331-0315):** Concept, literature search, writing, **A.A (0000- 0001-5797-1287):** Critical review, editing.

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RESEARCH ARTICLE

ARAŞTIRMA

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The safety and efficacy of leaving Titanium Elastic Nail tips outside the skin in pediatric femoral diaphyseal fractures

Çocuk femur diafiz kırıklarında Titanyum Elastik Nail uçlarının cilt dışında bırakılması güvenli ve etkin midir?

Necati Doğan[1*], Halil Büyükdoğan[2], Gürkan Çalışkan[3], Cemil Ertürk[3]

1.Basaksehir Çam and Sakura City Hospital, Department of Orthopaedics and Traumatology, Istanbul, Türkiye

2.Beykent University Hospital, Department of Orthopaedics and Traumatology, Istanbul, Türkiye

3.University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, Department of Orthopaedics and Traumatology, Istanbul, Türkiye

ABSTRACT

Aim: The aim of this study was to assess the efficacy of two different techniques involving titanium elastic nails (TEN) in pediatric femur diaphyseal fractures: leaving the nail tips outside the skin and placing them under the skin.

Patients and methods: We conducted a retrospective analysis of forty-six patients (comprising forty-seven fractures) who underwent TEN procedures for femoral diaphyseal fractures between January 2016 and July 2019. Patients were divided into two groups: Group 1 (nail tips left outside the skin) and Group 2 (nail tips left under the skin). We recorded patient age, gender, fracture side, and follow-up periods. Clinical assessments included hip and knee range of motion, presence of rotational or angular deformities, pin-site serous drainage, incision scars, and signs of infection. Radiological evaluations examined angulation, deformity, and length differences using anteroposterior (AP) and lateral radiographs. Implant removal times and complications were also documented.

Results: Group 1 consisted of twenty-one fractures, while Group 2 comprised twenty-six fractures. Age, gender, and fracture sides were similar between the two groups ($p>0.05$). However, the follow-up period was significantly longer in Group 2 ($p<0.05$), with a minimum follow-up period of nine months in both groups. Significant differences were observed in coronal and sagittal angulation measurements between the groups ($p<0.05$), although all measurements were within acceptable ranges for their respective age groups. Pin-site drainage was comparable between the two groups ($p>0.05$). Group 1 demonstrated a shorter implant removal time compared to Group 2 ($p<0.05$). Union was successfully achieved in all fractures in both groups, with no notable angulation defects, rotation defects, or shortening observed. No patients developed deep tissue infections.

Conclusions: In pediatric femur diaphyseal fractures, outpatient removal of implants without anesthesia by leaving the TEN tips outside the skin is feasible. This approach offers advantages similar to those of leaving the nail tips inside the skin in terms of union and angulation. However, pin-site infection remains a concern, which can be addressed through vigilant monitoring and parental education.

Keywords: Pediatric femur diaphyseal fracture, Titanium elastic nail (TEN), Elastic nail tip, Pin-site infection

ÖZ

Amaç: Bu çalışmanın amacı, çocuk femur diyafiz kırıklarında Titanyum Elastik Çivi (TEN) uygulamasında çivi uçlarının cilt dışında ve cilt altında bırakılmasının geriye dönük olarak değerlendirilmesidir.

Hastalar ve yöntem: Ocak 2016 ile Temmuz 2019 tarihleri arasında femur diyafiz kırığı nedeniyle TEN uygulanan 46 hasta (47 kırık) geriye dönük olarak incelendi. Hastalar, çivi uçları cilt dışında bırakılanlar için Grup 1 ve çivi uçları cilt altında bırakılanlar için Grup 2 olarak adlandırıldı. Yaş, cinsiyet, kırık tarafı ve takip süreleri kaydedildi. Klinik değerlendirme; kalça ve diz hareket açıklığı (ROM), rotasyonel veya açısal deformiteler, pin dibi akıntısı, insizyon izleri ve enfeksiyon belirtileri; radyolojik değerlendirme ise anteroposterior ve lateral radyografilerde angulasyon, deformite ve uzunluk farkları üzerine yapıldı. İmplant çıkarılma süreleri ve gelişen tüm komplikasyonlar değerlendirildi.

Bulgular: Grup 1'de 21 kırıkta (TEN uçları cilt dışında bırakıldı), Grup 2'de ise 26 kırıkta (TEN uçları cilt altında bırakıldı). Her iki grup da yaş, cinsiyet ve kırık tarafları açısından benzer dağılıma sahipti. Grup 2'nin takip süresi anlamlı derecede daha fazlaydı ($p<0,05$), ancak her iki grupta da minimum takip süresi 9 aydı. Her iki grupta da koronal ve sagittal angulasyon dağılımları arasında anlamlı farklılıklar ortaya çıktı ($p< 0,05$), ancak angulasyon değerleri her iki yaş grubunda kabul edilebilir sınırlardaydı. Pin dibi akıntısı her iki grupta da benzer dağılıma sahipti ($p > 0,05$). Grup 1, implant çıkarma süresi açısından Grup 2'ye kıyasla daha kısa bir sürede başarı sağladı ($p < 0,05$). Her iki gruptaki tüm kırıklarda sorunsuz kaynama sağlandı. Hastalarda dikkate değer angulasyon kusuru, rotasyon kusuru veya kısalık gözlenmedi. Hiçbir hastada derin doku enfeksiyonu gelişmedi.

Sonuç: Pediatrik femur diyafiz kırıklarında TEN uçlarının cilt dışında bırakılması, poliklinik şartlarında ve anestezi gerektirmeden implantların kısa sürede çıkarılmasını sağlamanın yanı sıra, çivi uçlarının içeride bırakılmasıyla benzer güvenlikte olduğu için oldukça avantajlıdır. Ancak, çivi dibi enfeksiyonu hala ciddi bir endişe kaynağıdır. Bu nedenle, bu sorunun sıkı takip ve ebeveyn eğitimi ile çözülebileceği kanaatindeyiz.

Anahtar Kelimeler: Çocuk femur diyafiz kırığı, Titanyum elastik çivi (TEN), Elastik çivi uçları, Pin dibi enfeksiyon

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*Corresponding Author: Necati Doğan, MD. Basaksehir Olimpiyat Bulvarı Yolu, 34480 Basaksehir, Istanbul, Türkiye Phone: +905531856544 / mail: drnecatidogan@gmail.com

Orcid: 0000-0001-9503-5676

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Introduction

Femoral diaphyseal fractures are the second most common fractures affecting the lower extremity in children, occurring at a rate of 20-26 per 100,000 children annually and accounting for 1-2% of all fractures in children. [1] The patient's age plays a crucial role in determining the appropriate treatment approach. While non-surgical methods such as Pavlik bandage, skeletal or skin traction, and pelvic-pedal casting are preferred for young children, surgical intervention has gained prominence in the last decade to mitigate the adverse effects of prolonged immobilization, enhance patient compliance, and promote early mobilization in older children.

Surgical treatment options for femoral diaphyseal fractures include plate-screw fixation and the use of rigid or elastic nails. These procedures can be performed using closed, minimally invasive, or open techniques. [2] The ability to frequently perform these procedures using a closed or minimally invasive approach has led to the popularity of elastic intramedullary nails. In pediatric femoral diaphyseal fractures, titanium elastic nails (TEN) are considered the standard of care for children aged 5-11. [3-4] However, a common issue associated with the use of TEN is the formation of excessive callus around the implant tips left under the skin, leading to difficulties during removal. Additionally, if left in place for an extended period, these tips can become palpable and cause skin irritation, most commonly. [5-6] Nonetheless, leaving the ends of TEN outside the skin, similar to the technique used for excluding K-wires in pediatric supracondylar humeral fractures, may be considered as an alternative. Similarly, studies have reported low rates of pin-site infection in pediatric humeral supracondylar fracture cases. [7-8]

Although the outside-the-skin technique has been reported in the performance of titanium elastic nails (TEN) for pediatric forearm double fractures, studies on its application in femoral fractures are lacking. [9-10] Therefore, our study aimed to retrospectively evaluate the use of nail tips outside and under the skin during TEN procedures performed in pediatric femoral diaphyseal fractures.

Patients and methods

Forty-six patients (47 fractures) who underwent titanium elastic nail (TEN) procedures for pediatric femoral diaphyseal fractures between January 2016 and July 2019 were retrospectively examined. Local ethics committee approval was obtained (KAEK/2018.12.79).

All pediatric patients who underwent TEN for femoral diaphyseal fractures were included in the study. Exclusion criteria comprised delayed fractures, pathological fractures, and patients with syndromes or comorbidities.

Patients whose TEN ends were left outside the skin constituted Group 1, while those with TEN ends left under the skin formed Group 2. Although closed reduction and casting were initially attempted for all patients, surgical intervention was recommended when radiological acceptance criteria were not met. All surgeries were performed by qualified surgeons. While some surgeons routinely left the TEN tips under the skin, others left them outside. The same implant material and system were utilized for all patients.

Surgical Technique

Group 1 (Outside the skin)

After the patient is sterilely draped in the supine position, medial and lateral entry points are marked under fluoroscopic guidance, slightly above the distal femur physis line. Mini-incisions are made to pass through the skin layers, reaching the distal femur. Medial and lateral nails of appropriate diameter are selected and inserted through the guide holes. The fracture line is typically reduced closed, but in cases of unsuccessful reduction, a mini-open approach may be employed, and reduction is achieved manually. Once the fracture line is stabilized with nails, the tips of the titanium elastic nails (TEN) are trimmed to protrude outside the skin, and the skin is sutured to cover the nail tips. (Figure 1) No splint is routinely applied postoperatively to any patient. During outpatient clinic follow-ups, passive hip and knee flexion exercises are encouraged, while weight-bearing is restricted until fracture healing is evident. Families are instructed to perform daily passive hip and knee flexion exercises. Immediate weight-bearing

is recommended for both groups once radiographs confirm bridging callus formation across the fracture site. In cases of pin-site infection, daily dressing changes and close monitoring are advised. If pin-site infection persists despite dressing changes, early removal of the affected implant and continued monitoring with a single TEN nail in a splint may be considered. If both implant tips are infected and pin-site discharge does not improve with serial dressings, early removal of both implants and continued follow-up in a splint are planned.

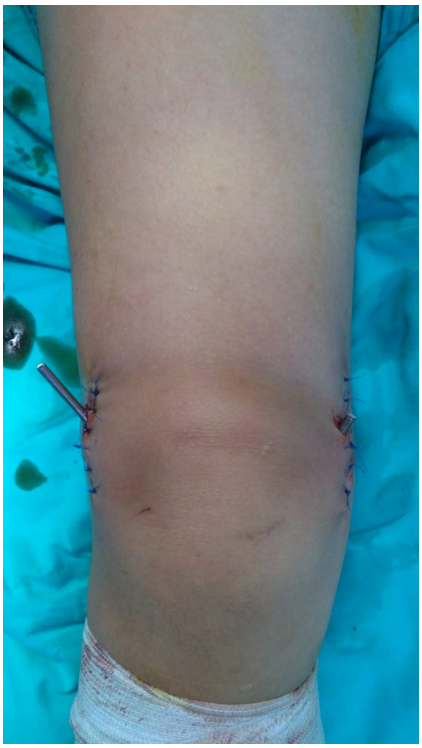

Figure 1: Appearance of TEN tips left outside the skin on the patient

After radiological union is confirmed, the titanium elastic nail (TEN) tips are removed in the outpatient clinic setting. Prior to the procedure, all patients and their relatives are informed, and their consent is obtained. If the implant cannot be removed or if the patient's tolerance is low, the procedure will be deferred and performed under operating room conditions. The implant is grasped with pliers and removed using gentle hammer taps. Following removal, the patient is advised to bear partial weight and is scheduled for follow-up appointments.

Group 2 (Under the skin)

The surgical procedure is completed in a manner similar to Group 1. The titanium elastic nail (TEN) tips are trimmed very close to the bone, left beneath the skin, and the incision is closed with sutures. During outpatient clinic follow-ups, knee and hip movement is permitted, but weight bearing is restricted until the fracture has healed. Once radiological union is confirmed, the TEN is removed under anesthesia, and the patient is readmitted to the hospital for an average duration of 6 months to 1 year.

Evaluation criteria

Age, gender, fracture side, and follow-up periods were recorded. Clinical evaluation included assessment of hip and knee range of motion (ROM), presence of rotational or angular deformities, pin-site serous drainage, incision scars, and signs of infection. Radiological evaluation involved examination of angulation, deformity, and length differences using anteroposterior (AP) and lateral radiographs. Implant removal times and all complications were assessed.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics 26 (IBM, Chicago, IL, USA). Descriptive statistics, including mean, standard deviation, median, frequency, ratio, and range, were calculated, and data distribution was assessed using the Shapiro-Wilk test. Student's t-tests were utilized to compare data between the two groups. A significance level of $p < 0.05$ was considered statistically significant for all analyses.

Results

The study included a total of 46 patients, comprising 15 boys and 31 girls, all of whom had unstable closed fractures. One patient in Group 1 presented with bilateral femoral diaphyseal fractures. In Group 1, TEN tips were left outside the skin for 21 fractures, whereas in Group 2, TEN tips were left under the skin for 26 fractures. The average age in Group 1 was 7.19 years, whereas in Group 2, it was 7.58 years. The male-to-female ratio was 0.42 in Group 1 and 0.52 in Group 2. Both groups demonstrated similar distributions in terms of age, gender, and fracture sides. ($p>0.05$) (Table I)

Table I: Demographic data of patients and parameters that are followed

		Outside the skin (Group 1) n= 20	Under the skin (Group 2) n = 26	p value
Age	Avg±Sd	7,19±1,5	7,58±2,14	0,471
	Min-Max	3-9	4-13	
Gender	Male	6	9	0,484
	Female	14	17	
Fracture side	Right	10	18	0,251
	Left	9	8	
	Bilateral	1	0	
Follow-up time (months)	Avg±Sd	12,47±4,3	24,38±8,86	0,001*
	Min-Max	9-23	9-42	
Coronal angulation	Avg±Sd	6,67±3,37	4,62±3,05	0,018*
	Min-Max	3,5-13,4	0,5-9,8	
Sagittal angulation	Avg±Sd	3,99±2,15	6,8±3,14	0,001*
	Min-Max	1,2-7,14	1,3-10,9	
Pin-site serous drainage	Yes	5	2	0,149
	No	16	24	
Implant removal times (weeks)	Avg±Sd	9,78±2,06	24,92±14,52	0,001*
	Min-Max	7-12	12-56	

*p< 0,05

When comparing the follow-up periods, the average follow-up period in Group 1 was 12.47 months, whereas in Group 2, it was 24.38 months. The follow-up period in Group 2 was significantly longer ($p<0.05$), although the minimum follow-up period in both groups was nine months. In terms of radiological evaluation, the average coronal angulation was 6.67 degrees in Group 1 and 4.62 degrees in Group 2, while the sagittal angulation was 3.99 degrees in Group 1 and 6.8 degrees in Group 2. There was a significant difference in the distribution of both coronal and sagittal angulation between the two groups ($p<0.05$), but all angulations were within acceptable limits for their respective age groups. (Table I)

In Group 1, superficial pin-site serous drainage occurred in 5 patients but resolved smoothly following implant removal. In Group 2, superficial pin-site serous drainage developed in 2 patients due to the migration of the implant tip from the skin. However, it regressed without any complications after implant removal. The distribution of pin-site drainage was similar between both groups. ($p>0.05$)

In Group 1, the implants were readily removed under outpatient clinic conditions after callus bridging was observed, with an average duration of 9.7 weeks (range: 7-12 weeks). Conversely, in Group 2, implant removal was performed at an average of 24 weeks (range: 12-56 weeks) by reopening the incision under general anesthesia to locate the implant tip. Group 1 achieved a significantly shorter implant removal time compared to Group 2. ($p<0.05$)

In Group 1, all cases were successfully removed under outpatient clinic conditions, obviating the need for an operating room. However, in 5 patients in Group 2, removal necessitated creating a window with an osteotomy in the bone due to excessive burying and closure of the tip with callus. Consequently, these patients were monitored with a splint for a period.

Union was successfully attained without complications in all fractures in both groups. No significant angulation defects, rotational abnormalities, or shortening were noted in any of the patients. Furthermore, complications such as malunion, pseudoarthrosis, and refracture did not occur. Additionally, there were no instances of deep tissue infection among the patients.

Discussion

In this study, we demonstrated that leaving titanium elastic nail (TEN) tips outside the skin does not yield clinically or radiologically different outcomes compared to those left under the skin. Moreover, both approaches exhibited similar infection rates. However, leaving the TEN tips outside the skin offers the advantage of easier and earlier removal without anesthesia in outpatient clinic settings, thereby reducing implant removal time.

Percutaneous pinning treatment using Kirshner wires is commonly employed and considered safe for various fractures. Additionally, percutaneous implants placed outside the skin, such as external fixators or Ilizarov devices, are utilized in clinical practice. Although pin site infections associated with Kirshner wires or fixator pins have been reported, the incidence of severe infections is generally low. [11] For instance, in a multicenter study by Combs et al. [7], which included 369 supracondylar fracture patients treated with chrome-cobalt or titanium implants, only three

cases of pin site infection (0.81%) were identified. The authors recommended preoperative antibiotic prophylaxis, minimizing the duration of pin fixation, and early cast changes to mitigate infection risk. Another study suggested that leaving Kirshner wires outside the skin reduced the need for hospital admissions compared to burying them under the skin and did not result in significant clinical or radiological differences. [12] However, in our study, we observed a higher incidence of pin site infections than expected. Specifically, five patients with TEN tips left outside the skin developed pin site infections, while two patients with TEN tips left inside experienced pin migration during follow-up, resulting in pin site infections. Although these infections were superficial, the occurrence rates appear elevated relative to the study population size.

The studies by Kelly et al. [8] and Dinçer et al. [9] closely resemble our study in terms of methodology and focus. Kelly et al. retrospectively analyzed 339 patients with forearm diaphyseal fractures treated with titanium elastic nails (TEN). They compared outcomes between patients with buried versus exposed TEN tips and found no significant differences in infection rates, refracture incidence, or other complications. Similarly, Dinçer et al. conducted a current and prospective study involving 192 patients with forearm diaphyseal fractures treated with TEN. They observed that leaving the pin tips exposed was associated with shorter implant removal times and a lower incidence of skin irritation and embedded pins compared to burying the pins. Although superficial infections were detected in a small percentage of cases with exposed pin tips, the overall complication profile was comparable between the two groups, suggesting that leaving the ends of the implant exposed is safe. While our study did not directly compare fracture union times, we found that leaving the implant tips outside the skin facilitated earlier removal of the implant without anesthesia in outpatient clinic settings. Conversely, cases where the implant tips remained inside necessitated postponing the removal procedure due to the inability to remove the implant in outpatient settings. This was often due to concerns about repeat anesthesia procedures, lack of infection concerns at the nail site, and the availability of appropriate surgical conditions for the removal procedure.

The findings from our study align with those of Kelly et al. [8] and Dinçer et al. [9], particularly regarding the challenges associated with leaving the implant tip under the skin. In our study, we also encountered difficulties related to the length of the implanted tip, where leaving it too short could lead to removal problems, while leaving it too long could cause skin irritation and discomfort. While forearm TENs have shown low infection rates when the implant tip is excluded, our study revealed a superficial infection rate of approximately 25%. Several factors may contribute to this higher infection rate in femoral TENs. Firstly, the femur is a weight-bearing bone subjected to significant stress and load compared to the forearm, which may increase the likelihood of infection. Additionally, the care and maintenance of lower extremities are inherently more complex than that of upper extremities, potentially contributing to the higher infection rates observed. The proximity of the femur to the urogenital area may also increase the risk of infection. Furthermore, the union time following femoral TEN procedures is longer compared to forearm TENs, resulting in the implant tip remaining exposed for a prolonged period. This prolonged exposure may increase the likelihood of infection, especially considering that the femur takes longer to fuse compared to forearm bones. However, it's worth noting that the superficial infections observed in our study resolved promptly following implant removal.

In adults, internal implants are typically left in place after osteosynthesis unless there are specific reasons for removal. However, in pediatric patients, implants are often designed to accommodate growth, or they may need to be removed post-osteosynthesis to prevent interference with skeletal development. Unlike external implants, which can be safely removed in outpatient clinic settings, internal implants usually require removal in the operating room. In a retrospective study by Simanovsky et al. [10], 143 children who underwent femur and forearm TEN implant removal were assessed. The study found that in 16 patients, implant removal was necessary due to bone embedding and skin irritation. Moreover, the implant could not be removed in 3 children, and refracture occurred

in 2 children after implant removal. This study prompted discussions regarding the necessity of implant removal in pediatric patients. In our study, conducted on the group where the TEN tips were left under the skin, we encountered challenges such as excessive burial and bone coverage of implants in 5 patients, leading to difficulties during implant removal.

Our study demonstrates that radiological evaluation shows angulations within acceptable ranges, indicating that leaving the ends of the implant inside or outside does not biomechanically disrupt the effectiveness of the implant on reduction. Both coronal and sagittal angulations are equally affected by this approach. Clinically, successful outcomes regarding joint range of motion, rotation, and leg length differences in both groups indicate the efficacy of TEN treatment, unaffected by whether the TEN tips are left under or outside the skin.

However, it's essential to acknowledge the limitations of our study. Being retrospective and having a minimum follow-up period of nine months, along with the limited number of cases, are notable weaknesses. Therefore, prospective, randomized, and more extensive studies are warranted to provide more robust evidence for making decisions on this matter.

Conclusion

In pediatric femur diaphyseal fractures, leaving the TEN tips outside the skin enables quick removal of implants under outpatient clinic conditions without anesthesia. This approach offers advantages, as union or angulation issues are comparable to when nail tips are left inside. Nevertheless, the risk of pin-site infection remains a significant concern, which can be addressed through vigilant monitoring and parental education.

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Ethics Committee Approval: Local ethics committee approval was obtained. (KAEK/2018.12.79)

ORCID and Author contribution: N.D. (0000-0001-9503-5676): Concept and Design, Data Collection, Interpretation of Results, Literature Search, Writing, Critical Review. Final Approval, **H.B. (0000-0002-0202-444X):** Data Collection, Literature Search, Writing. Editing **C.E. (0000-0002-9225-917X):** Concept and Design, Data Collection, Critical Review. Final Approval **G.Ç. (0000-0002-4612-1700):** Data Collection, Interpretation Literature Search, Critical Review. Final Approval.

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RESEARCH ARTICLE

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Effect of Gallic Acid on PTZ-induced Neurotoxıcıty, Oxidative Stress and Inflammation in SH-SY5Y Neuroblastoma Cells

SH-SY5Y Nöroblastoma Hücrelerinde PTZ ile Oluşturulan Nörotoksisite, Oksidatif Stres ve İnflamasyon Üzerine Gallik Asidin Etkisi

Yener Yazğan[1*]

1.Department of Biophysics, Faculty of Medicine, Kastamonu University, Kastamonu, Türkiye

ABSTRACT

Aim: Human neuroblastoma cell lines are widely used to elucidate the cellular and molecular mechanisms of neurotoxicants and to facilitate the prioritization of in vivo testing. Pentylenetetrazole (PTZ) is a tetrazole derivative. Although PTZ is the most commonly used chemical to create an in vivo and in vitro epilepsy (EP) model, its mechanism of action in neuronal cells has not been fully elucidated. Gallic acid (GA) has broad biological properties such as antioxidant, anti-microbial, and anti-inflammatory activities. This study aimed to investigate the effect of GA on PTZ-induced neurotoxicity in neuroblastoma cells.

Methods: For the study, four groups were formed from SH-SY5Y neuroblastoma cells as control (C), GA (100 µM), PTZ (30 µM), and PTZ+GA. In the study, total antioxidant and oxidant status (TAS and TOS), inflammatory cytokines (TNF α, IL 1β, and IL 6), lipid peroxidation levels as malondialdehyde (MDA), glutathione peroxidase (GSHPx), and glutathione (GSH) levels in the SH-SY5Y neuroblastoma cells were determined.

Results: The results showed that PTZ treatment caused neurotoxicity in the neuroblastoma cell line and increased TOS, TNF α, IL 1β, IL 6, and MDA levels while decreasing TAS, GSH, and GSHPx levels. This situation improved with GA treatment.

Conclusion: As a result, it was determined that GA treatment showed a protective effect in the PTZ-induced neural toxicity model in SH-SY5Y human neuroblastoma cell lines.

Keywords: Neurotoxicity, SH-SY5Y neuroblastoma cell, Gallic acid, Pentylenetetrazole

ÖZ

Amaç: İnsan nöroblastoma hücre hatları, nörotoksik maddelerin hücresel ve moleküler mekanizmalarını aydınlatmak ve in vivo testlerin önceliklendirilmesini kolaylaştırmak için yaygın olarak kullanılmaktadır. Pentilenetetrazol (PTZ) bir tetrazol türevidir. PTZ, in vivo ve in vitro epilepsi (EP) modeli oluşturmak için en yaygın kullanılan kimyasal olmasına rağmen, nöronal hücrelerdeki etki mekanizması tam olarak aydınlatılamamıştır. Gallik asit (GA) antioksidan, anti-mikrobiyal ve anti-enflamatuar aktiviteler gibi geniş biyolojik özelliklere sahiptir. Bu çalışma, GA'nın nöroblastoma hücrelerinde PTZ kaynaklı nörotoksisite üzerindeki etkisini araştırmayı amaçlamıştır.

Yöntem: Çalışma için SH-SY5Y nöroblastoma hücrelerinden kontrol (K), GA (100 µM), PTZ (30 µM) ve PTZ+GA olmak üzere dört grup oluşturulmuştur. Çalışmada SH-SY5Y nöroblastoma hücrelerinde toplam antioksidan ve oksidan durumu (TAS ve TOS), inflamatuvar sitokinler (TNF α, IL 1β ve IL 6), glutatyon peroksidaz (GSHPx), glutatyon (GSH) seviyeleri ve malondialdehit (MDA) olarak lipid peroksidasyon seviyeleri belirlenmiştir.

Bulgular: Sonuçlar PTZ tedavisinin nöroblastoma hücre hattında nörotoksisiteye neden olduğunu ve TOS, TNF α, IL 1β, IL 6 ve MDA seviyelerini artırırken TAS, GSH ve GSHPx seviyelerini azalttığını göstermiştir. Bu durum GA tedavisi ile düzelmiştir.

Sonuç: Sonuç olarak, GA tedavisinin SH-SY5Y insan nöroblastom hücre hatlarında PTZ kaynaklı nöral toksisite modelinde koruyucu bir etki gösterdiği belirlenmiştir.

Anahtar Kelimeler: Nörotoksisite, SH-SY5Y nöroblastom hücresi, Gallik asit, Pentilenetetrazol

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*Corresponding Author: Yener Yazğan, Department of Biophysics, Medical Faculty, Kastamonu University, Kastamonu, Türkiye. Phone: +90366 280 72 08/ mail: yener8275@hotmail.com

ORCID: 0000-0002-5613-6906

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Introduction

Epilepsy (EP), often characterized by recurrent epileptic seizures, consists of various neurological conditions [1]. Although many antiepileptic drugs are used in the clinic to treat EP, approximately 30% of patients still cannot control their seizures medically [2]. Withal, many studies have shown that recurrent and prolonged seizures often lead to neuronal damage [3]. Despite the high prevalence and extensive research on EP, a common neurological disorder, the cellular and molecular mechanisms underlying epileptogenesis and neuronal injury remain unclear. The human SH-SY5Y neuroblastoma cell lines are widely used to elucidate neurotoxic substances' cellular and molecular mechanisms and to prioritize in vivo testing [1,4]. Epileptic activity in vivo and in vitro experimental models is mainly induced by the local administration of epileptogenic drugs, including the widely used pentylenetetrazole (PTZ) [5,6].

PTZ, a bicyclic tetrazole derivative, is a GABA-A (γ-aminobutyric acid type A) receptor antagonist and causes excitation in neurons [7]. Due to its stimulating effect, PTZ is the most widely used chemical to create an in vivo and in vitro EP model [1,3,5,6]. Although neurobiological processes and structural changes resulting from stimulation with PTZ have been investigated, the mechanisms that trigger neurotoxicity have not been fully elucidated. Extensive experimental studies have shown that inflammation and oxidative stress are crucial in developing neurological diseases [1,8,9]. Strengthening neuronal cell defense against oxidative stress and inflammatory processes with exogenous antioxidant-anti-inflammatory substances can provide adequate protection [10]. Therefore, improving antioxidant-anti-inflammatory compounds from natural sources is of great scientific interest.

Gallic acid (GA) has broad biological properties such as antioxidant, anti-microbial, and anti-inflammatory activities [11]. Some recent studies have demonstrated the practical activity of phytoconstituents such as GA in preventing neuronal damage (3,4,5-trihydroxy benzoic acid) [11]. GA is a flavonoid found in natural foods such as sumac, green tea, witch hazel, and oak bark and has critical biological effects [12,13]. Recently, interest in GA has increased due to its different effects, such as anticancer, anti-inflammatory, and antioxidant [13-15]. However, more research must be done on its neuroprotective effect [8,10,13]. In addition, the mechanism of its protective effect on nerve cells has yet to be understood.

PTZ treatment has been reported to cause neuronal damage in experimental in vitro [1,3] and in vivo [16,17]. However, the mechanisms by which PTZ triggers cell damage in EP models remain unclear. Inflammation and oxidative stress often play a role in the pathology of secondary neuronal damage following EP [18,19]. Experimental studies suggest that GA reverses oxidative stress and suppresses inflammation [8,10]. However, the roles and mechanisms of action of GA on PTZ-induced neuronal damage are not yet known. Although there are limited studies investigating PTZ-induced neural toxicity in human neuroblastoma cells, there is no research examining the regulatory role of GA in this process, which makes this study original.

This study aimed to investigate the effect of PTZ, widely used in the experimental neural toxicity model, on human neuroblastoma cells and the curative effect of GA.

Materials and Methods

Chemicals and ELISA Kits

Gallic acid (Cat; G7384) was obtained from Sigma Aldrich C. (St Louis, USA). Pentylenetetrazole (Cat; P6500) was purchased by Sigma Aldrich C. (St Louis/USA). IL 6 (Cat; KET6017), IL 1β (Cat; KET6013), and TNF α (Cat: KET6032) were purchased from Abbkine/Scientific C. (Wuhan, China). SH-SY5Y cells (Cat; CRL-2266) were purchased from ATCC (VA, USA). Total Oxidant and Total Antioxidant Capacity (TOS product no: RL0024 and TAS product no: RL0017) ELISA kit was obtained from Rel Assay (Gaziantep/Türkiye). Other chemicals used in glutathione, glutathione peroxidase, and lipid peroxidation analyses were purchased from Sigma Chemical Inc. (St. Louis, USA).

Cell Culture and Experimental Groups

A growth medium was prepared for the cells

used in the research according to the instructions provided by the seller. FBS (Cat; SV30160.03, cytiva) (10 %) and penicillin/ streptomycin (Cat; LM-A4118, biosera) (1 %) were added to equivalent volumes of Ham's F12 (Cat; L0135, biowest) and DMEM (Cat; L0064, biowest) as growth medium contents. Cells (6-8 passages) previously purchased from ATCC and stored in a nitrogen tank were used. The cells taken from the nitrogen tank were passaged, and after the cells reached 80-85% confluence, they were divided into four groups, and this process was repeated. Cells were cultured in 25 cm2 culture flasks in an incubator at 37 °C under a 5 % CO_2 atmosphere. Human SH-SY5Y neuroblastoma cells were divided into four groups and incubated according to the experimental procedure. PTZ and GA were freshly prepared on the experimental days.

Control (C) group (n=5), no treatment was applied to the control group.

GA group (n=5), Cells were added 100 µM GA and incubated for 24 hours [20].

PTZ group (n=5), cells were added 30 µM PTZ and incubated for 24 hours [1].

PTZ+GA group (n=5), the cells were incubated by PTZ (30 µM) and GA (100 µM) for 24 hours.

After the incubation period was completed, the cells were washed with fresh 1xPhosphate Buffered Saline (PBS, Biochrom/Germany), and 0.25 % Trypsin-EDTA (Sigma-Aldrich) was applied to separate the cells from the flask floor. After completing the experimental steps, analyses were performed for all groups.

Preparation of Cells Homogenates

For each group, cells were transferred into separate sterile falcon tubes and centrifuged according to the kit procedure (1000 rpm and 20 min). After centrifugation, the supernatants on the top of the falcon tubes were removed with the help of an automatic pipette, the cells were suspended in PBS, and a cell suspension with a density of approximately 1×10^6 cells/ml was obtained. The cell structure was lysed (PBS) by freeze-thaw repetition, and the mixture was centrifuged at 4000 rpm for 10 minutes at 4 °C after removing the cytoplasmic components. The supernatant remaining at the top of the falcon tubes was removed with pipettes and taken in Eppendorf tubes for analysis. The Bradford protein assay kit (Merck-Millipore) measured total protein levels in the groups.

Analyses

Measurement of Total Oxidant-Antioxidant and Inflammatory Cytokines Levels in the SH-SY5Y Neuroblastoma Cells

PTZ-induced toxicity induction of inflammatory cytokines (TNF α, IL 1β, and IL 6) ELISA kits determined levels in the supernatants of the SH-SY5Y cell line. For the analyses, supernatants were first incubated at 37 °C for 60 minutes by the protocols specified by the companies for commercial kits and then placed in 96-well plates with automatic pipettes. The supernatant and standard samples placed on the plate were incubated for 60 minutes, followed by washing steps, and then staining solutions were added and incubated for 15 minutes. A stop solution was added at the end of all these procedures, and absorbance values were read at 450 nm on an ELISA (BioTek ELx808™) microplate reader [21].

PTZ-induced toxicity induction of Total antioxidant status (TAS) and Total oxidant status (TOS) ELISA kits determined levels in the supernatants of the SH-SY5Y cell line. For TAS analysis, cell culture supernatants were used, and culture samples, kit standard (mmol Trolox eq/L), and dH_20 were mixed with Reagent 1 (Buffer, 200 µL) in 96-well plates and incubated for 5 min according to the manufacturer's protocols. The absorbance was measured at 660 nm (the first absorbance of the sample). Then, Reagent 2 (Color ABTS Radical Solution, 30 µL) was added, and mixtures were incubated at 37 °C for 5 min; an ELISA microplate reader monitored absorbance at 660 nm (second absorbance of the sample). Each sample data was calculated using the kit's standard (equivalent to 1 mmol/L of Trolox). For TOS analysis, cell culture supernatants were used. For the dilution step, 5 µL of Standard 2 and 1 mL of distilled water were transferred to Eppendorf and vortexed. Then, 5 µL of this solution was transferred to Eppendorf, and 20 mM H_2O_2 was prepared by adding 1 mL of water. For TOS analysis, Reagent 1 (Assay buffer, 200 µL) was added to each well, and absorbances

were measured at 530 nm (first absorbance of the sample). Next, Reagent 2 (Prochromogen solution, 10 µL) was added, and samples were incubated for 5 min at 37 °C. Finally, absorbance was monitored at 530 nm using an ELISA microplate reader (second absorbance of the sample). The assay was calibrated with hydrogen peroxide, and the results are expressed in micromolar hydrogen peroxide equivalents per litre (µmol H_2O_2 equivalents/L). The percentage ratio of the TOS to the TAS was accepted as the oxidative stress index (OSI), an indicator of the degree of oxidative stress. For calculations, the resulting unit of TAS, mmol Trolox eq/L, was converted to µmol Trolox eq/L, and the OSI value was calculated using the following formula: OSI = [TOS (µM H_2O_2 eq/L) / TAS (µmol Trolox eq /L)] × 100.

Measurement of Lipid Peroxidation, Glutathione, and Glutathione Peroxidase levels in the SH-SY5Y Neuroblastoma Cell

Lipid peroxidation activity, which is known as malondialdehyde (MDA) release in PTZ-induced nephrotoxicity in SH-SY5Y human neuroblastoma cells, was determined by thiobarbituric acid (TBARS) reaction in a highly sensitive spectrophotometer (V-730 UV-Visible Spectrophotometer, Japan) according to the method of Placer et al. All cell groups were reconstituted with 1/9 (2.25 ml) TBARS solution. The experiment used a mixture of 0.25 ml phosphate buffer and 1/9 of TBARS as a blind. Samples and blind were kept in 100 °C water for 20 minutes [22,23]. It was then cooled on ice and centrifuged at 1000 g for 5 min. The upper pink liquid was taken with an automatic pipette and read against the blind in a spectrophotometer at 532 nm wavelength in a 1 cm light transmission cuvette. The standard was standard: 1, 1, 1, 3, 3 tetraethoxy propane solution prepared in the same proportions. Values were determined as µmol/g protein.

Glutathione (GSH) levels of SH-SY5Y human neuroblastoma cells were determined spectrophotometrically at 412 nm using the Sedlak and Lindsay method [24]. The cells (10^6 cells per mL) were transferred to sterile falcon tubes with the help of an automatic pipette and centrifuged to separate the proteins after mixing with 10% trichloroacetic acid. After centrifugation, 0.1 ml of the supernatant remaining on the falcon tube was taken and placed in a glass tube, 0.5 mL 5.5-dithiobis (2-nitrobenzoic acid), 2 mL phosphate buffer (pH 8.4), and 0.4 mL distilled water were added. The resulting sample was read at 412 nm in a spectrophotometer. Values were determined as µmol/g protein.

Glutathione peroxidase (GSHPx) levels of SH-SY5Y human neuroblastoma cells were determined spectrophotometrically at 412 nm by Lawrence and Burk's method [25]. The activity of GSHPx was expressed as international units (IU) of oxidized glutathione/g protein. Total protein in cells was assessed spectrophotometrically at 595 nm using Bradford reagent.

Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Data analyses were performed with the SPSS (version 17.0, software, USA) program. One-way ANOVA was used to evaluate the differences between the groups. Post-hoc Tukey test was used in all data with a statistically significant difference. $p \leq 0.05$ was considered statistically significant.

Results

Effect of Gallic Acid on TOS and TAS Levels in SH-SY5Y Neuroblastoma Cells

This study measured changes in TOS and TAS levels between experimental groups with commercial Elisa kits. Figure 1 shows that GA treatment modulates the decrease in TAS levels (Figure 1B) and the increase in TOS levels (Figure 1A) in PTZ-induced SH-SY5Y cells. A significant increase in TOS and OSI levels (Figure 1A and 1C) was observed in the PTZ-treated group was compared to C, GA, and PTZ+GA groups ($p \leq 0.05$), and in parallel, a significant decrease in TAS levels (Figure 1B) was observed in the PTZ-treated group was compared to C, GA and PTZ+GA groups ($p \leq 0.05$). The decrease in TAS levels and increase in TOS levels were regulated by GA treatment.

Effect of Gallic Acid on Inflammatory Cytokines Levels in SH-SY5Y Neuroblastoma Cells After PTZ-induced Cytotoxicity

The changes in inflammatory cytokines (TNF α, IL 1β, and IL 6) levels in cells against PTZ-induced cytotoxicity of gallic acid in the groups formed were measured with the Elisa kits. GA treatment modulated PTZ-induced inflammation (TNF α, IL 1β, and IL 6) levels in the SH-SY5Y neuroblastoma cells are shown in Figure 2. When the PTZ-induced treated group was compared to the C, GA, and PTZ+GA groups between the groups, it was observed that the IL 1β, IL 6, and TNF α levels (Figure 2A, 2B, and 2C) increased considerably ($p \leq 0.05$). This situation was regulated by GA treatment.

The Gallic Acid Treatment Attenuated the PTZ-induced Changes in GSH, GSHPx, and MDA Levels.

The changes in GSH, GSHPx, and MDA levels in cells against PTZ-induced cytotoxicity of GA in the groups formed were measured spectrophotometrically. GA treatment modulated PTZ-induced lipid peroxidation and impaired antioxidant balance levels in the SH-SY5Y neuroblastoma cells are shown in Figure 3. When the PTZ-induced treated group was compared to the C, GA, and PTZ+GA groups between groups, it was observed that the GSH level (Figure 3A) decreased considerably ($p \leq 0.05$). GSHPx levels (Figure 3B) were significantly reduced between the groups when the PTZ-induced treated group was compared to the C, GA, and PTZ+GA groups ($p \leq 0.05$). MDA levels (Figure 3C) were significantly increased between the groups when the PTZ-induced treated group was compared to the C, GA, and PTZ+GA groups ($p \leq 0.05$). This situation was regulated by GA treatment.

Discussion

Abnormal electrical discharges in the brain characterize EP [1]. Generally, epileptiform activity is induced by local administration of epileptogenic drugs such as PTZ, widely used in both in vitro and in vivo experimental models [3,6]. Numerous experimental and clinical studies report that epileptic seizures cause neuron damage [16,26]. However, the mechanisms by which PTZ induces cell damage are unclear, so experimental models of PTZ-induced EP are attractive. It has been shown in some animal studies that oxidative stress has an essential role in the etiology of EP [1,16]. In the rat EP model created with PTZ, MDA levels increased in the hippocampus, while SOD and GSHPx levels decreased [16]. A similar study observed increased MDA levels in rats induced by PTZ, while a significant decrease was observed in CAT, SOD, and GSH levels [17]. An increase in lipid peroxidation, neutrophil infiltration, and oxidative stress parameters was reported in another PTZ-induced rat brain injury and memory impairment model [9,18]. As we highlighted, many studies emphasize that PTZ application causes neuronal damage in cell culture models performed in vitro [1,3,5] or animal models performed in vivo [16,17]. This study investigated how inflammation and oxidative stress markers changed in human SH-SY5Y neuroblastoma cells after PTZ administration. It was found that the levels of TOS and apoptosis were increased in PTZ-induced human SH-SY5Y neuroblastoma cells, whereas the levels of TAS were significantly decreased [27].

Our study observed that the TOS level increased considerably in the PTZ group compared to the C group, whereas the TAS level decreased significantly. Moreover, in our research, while MDA levels increased in the PTZ group, GSH and GSHPx levels decreased. In our study, which aimed to determine the mechanisms that trigger neurotoxicity due to stimulation with PTZ, we also examined the parameters of inflammation. We determined that inflammatory cytokines (IL 1β, TNF α, and IL 6) levels were significantly increased in the PTZ group compared to the other groups. Thus, we demonstrated significant increases in inflammatory cytokine levels in a PTZ-induced in vitro model of EP. Consistent with our results, Khatoon et al. reported that TNF α and IL 6 levels in the cortex and hippocampus of mice induced by PTZ were significantly increased compared to the C group [28]. In addition, in the EP model created in HT-22 cells, an increase in inflammatory cytokines (TNF α, IL 1β, and IL 6) levels was observed in the cells in the PTZ group [6]. Similarly, Ahlatçı et al. showed a significant increase in inflammatory cytokines (TNF α, IL 1β, and IL 6) levels in PTZ-induced cells [1].

There are limited studies on the neuroprotective effect of GA, which has essential effects such as anticancer, anti-inflammatory, and antioxidant

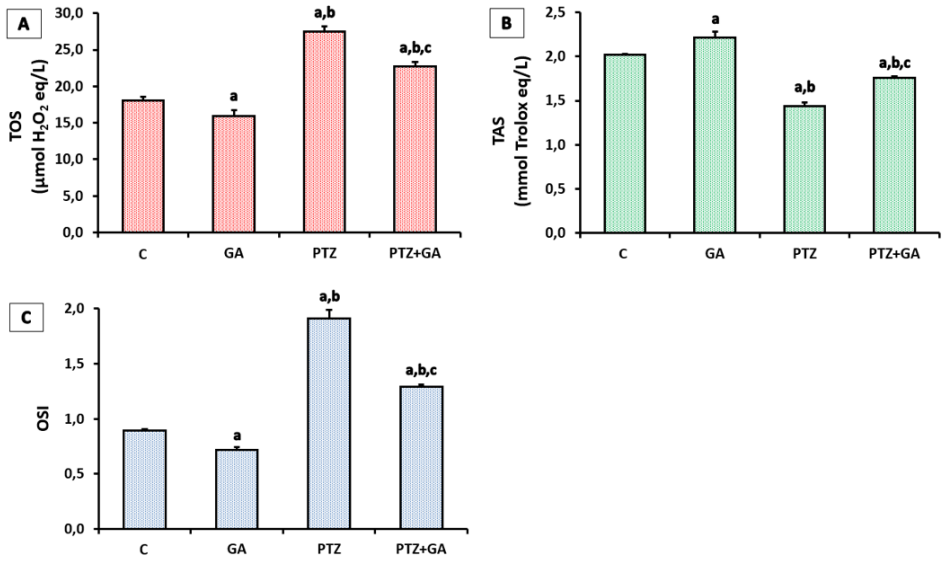

Figure 1. The effect of PTZ and GA treatment on TOS (A), TAS (B), and OSI (C) levels (mean ± SD). (ap≤ 0.05 vs. C group, bp≤ 0.05 vs. GA group, cp≤ 0.05 vs PTZ group).

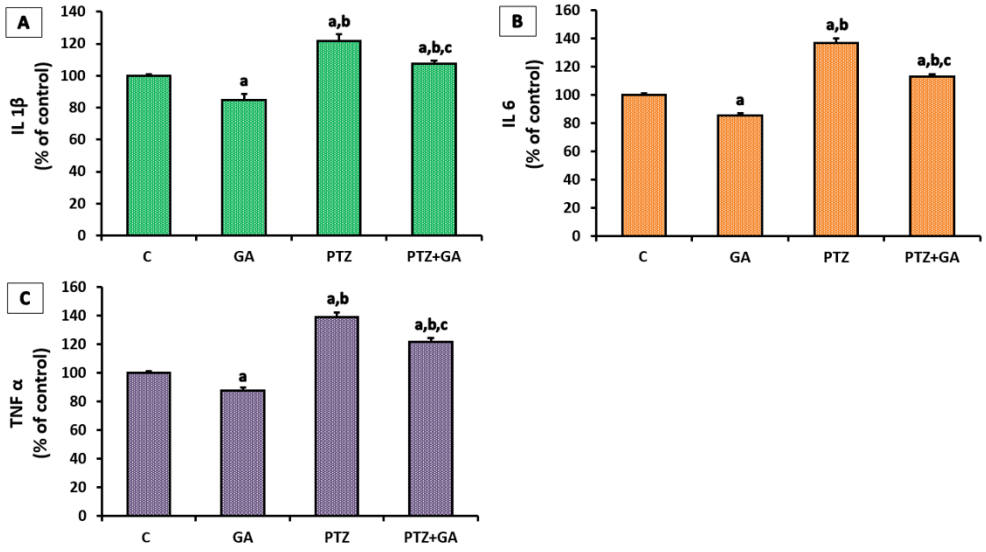

Figure 2. The effect of PTZ and GA treatment on IL 1β (A), IL 6 (B), and TNF α (C) levels (mean ± SD). (ap≤ 0.05 vs. C group, bp≤ 0.05 vs. GA group, cp≤ 0.05 vs PTZ group).

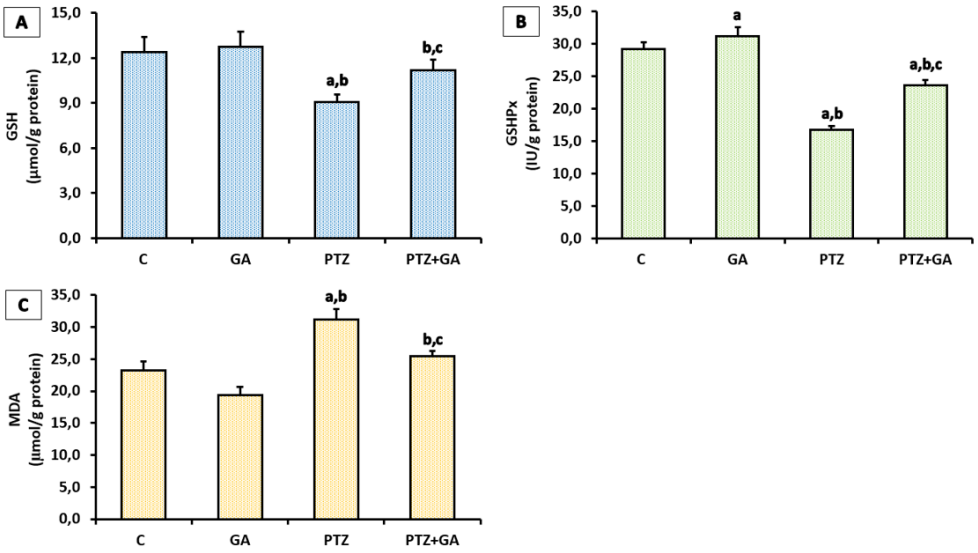

Figure 3. The effect of PTZ and GA treatment on GSH (A), GSHPx (B), and MDA (C) levels (mean ± SD). (ap≤ 0.05 vs. C group, bp≤ 0.05 vs. GA group, cp≤ 0.05 vs PTZ group).

[15,29,30]. In this study, we investigated the possible mechanism of the protective effect of GA on nerve cells in an in vivo experimental EP model. For this purpose, we administered GA treatment to groups with and without PTZ. Our study observed that GA incubation with PTZ reduced oxidative stress and suppressed inflammation. We showed that the use of GA in the GA group increased the GSHPx and GSH levels and decreased the MDA level compared to the PTZ group. Moreover, in line with the literature, inflammatory cytokines (TNF α, IL 1β, and IL 6) levels decreased in the same group [31,32]. Like our results, Maurya et al. determined that GA treatment significantly reduced lung, liver, kidney, and spleen MDA levels and showed significant improvement in SOD activity in septic mice [30]. Similarly, inflammatory cytokines (TNF α, IL 1β, and IL 6) levels decreased in the same group. We also found a significant improvement in MDA, GSH, and GSHPx levels in the PTZ+GA group compared to the C group. However, there was a significant improvement in oxidative parameters compared to the C group. Similarly, there was a significant improvement in inflammatory cytokine (TNF α, IL 1β, and IL 6) levels compared to the C group. This study showed that GA improved PTZ-induced oxidative stress and inflammation. Our study proved that GA exerts neuroprotective effects through antioxidant and anti-inflammatory mechanisms in SH-SY5Y cells in an in vitro EP model.

Lımıtatıons: This study used only the SH-SY5Y human neuroblastoma cell line to model EP with PTZ. In addition, studies investigating signaling pathways at the molecular level are needed to understand better how PTZ affects molecular mechanisms.

Conclusion: There is current research showing that EP attacks cause neurotoxicity. Since attacks cannot be prevented entirely in many patients, minimizing the neuronal damage caused by attacks would be a correct additional treatment approach for EP. In this context, it is vital to determine the mechanisms underlying neuronal damage and find treatments that will reduce neuronal damage.

This study showed that in an in vitro EP model, PTZ induced neurotoxicity in SH-SY5Y neuroblastoma cells by disrupting the oxidant/antioxidant balance and increasing the release of inflammatory cytokines. In addition, the regulatory effectiveness of GA was determined, and essential preclinical data was provided to the literature. Although these data show the possibility of using natural substances such as GA to reduce the damage that may occur during attacks in EP patients, further preclinical research is needed.

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Ethics Declarations: The current study has no study with human and human participants. The study is not subject to ethics committee approval.

AORCID and Author Contribution: **YY (0000-0002-5613-6906)** was responsible for formulating the hypothesis, analyses and writing the report.

Abbreviations

DMEM, Dulbecco's Modified Eagle Medium

FBS, Fetal Bovine Serum

GA, Gallic acid

GSHPx, Glutathione peroxidase

GSH, Glutathione

MDA, Malondialdehid

ROS, Reactive oxygen species

SH-SY5Y, Human neuroblastoma cell line

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RESEARCH ARTICLE

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Assessment of YouTube Videos on Frozen Shoulder: A Quality Analysis Using DISCERN and JAMA Scoring Systems

DISCERN ve JAMA Puanlama Sistemleri Kullanılarak YouTube Videolarının Donuk Omuz Üzerine Güvenilirliğinin Değerlendirilmesi

Tolgahan Cengiz[1], Şafak Aydın Şimşek[2]*, Ahmet Ersoy[3], Hüseyin Sina Çoşkun[2], Ahmet Pişkin[2]

1.Inebolu State Hospital, Department of Orthopedics and Traumatology Kastamonu,Türkiye
2.Ondokuz Mayis University, Faculty of Medicine, Department of Orthopedics and Traumatology, Samsun, Türkiye
3.Turhal State Hospital, Department of Orthopedics and Traumatology, Tokat, Türkiye

ABSTRACT

Aim: Frozen shoulder, characterized by synovial inflammation and joint capsule fibrosis, impacts shoulder mobility and comfort. With the rise of online health information seekers, assessing the credibility of YouTube videos on frozen shoulder is crucial. This study aims to explore potential differences between physician and non-physician contributors by assessing the quality of Youtube videos using the DISCERN and JAMA scoring systems.

Methods: The first 50 YouTube videos found by searching with the word "Frozen shoulder" were examined; Short, repetitive titles and non-English content were not included in the study. Videos were categorized by content type, uploader, and key metrics of the videos were recorded. Two observers independently scored the videos using DISCERN and JAMA systems.Statistical analysis was performed, including Mann-Whitney tests and Spearman correlation..

Results: While 45 of the 50 videos contained real images, 5 were animations. Physiotherapists were the most contributing group (40%), and 60% of the videos contained general information about frozen shoulder. Considering the average DISCERN and JAMA scores, videos were mostly rated poor in quality. No statistically significant differences were found between the videos uploaded by physicians and non-physicians. Observer agreement was excellent.

Conclusion: Internet users searching for information about frozen shoulder face difficulties in distinguishing reliable content. Healthcare professionals should share videos with accurate information and direct patients to reliable online resources.

Key Words: frozen shoulder, adehsive capsulitis, patient education, information, youtube

ÖZ

Amaç: Donuk omuz, sinoviyal iltihap ve eklem kapsül fibrozisinden kaynaklandığı düşünülen, omuz hareketini ve konforunu etkileyen bir durumdur. İnternet üzerinde sağlık bilgisi arayanların sayısının artmasıyla birlikte, YouTube videolarının donuk omuz üzerine güvenilirliğinin değerlendirmesi önemli bir durum olmuştur. Bu çalışma, DISCERN ve JAMA puanlama sistemlerini kullanarak Youtube videolarının kalitesini değerlendirerek, doktor ve doktor olmayan katkı sahipleri arasındaki potansiyel farkları keşfetmeyi amaçlamaktadır.

Yöntem: "Frozen shoulder" kelimesi ile arama yapılarak bulunan ilk 50 YouTube videosu incelendi; kısa, tekrarlayan başlıklar ve İngilizce olmayan içerikler çalışmaya dahil edilmedi. Videolar içerik türüne, yükleyiciye göre kategorize edildi ve videoların temel özellikleri kaydedildi. İki gözlemci, videoları DISCERN ve JAMA sistemleri kullanarak bağımsız olarak puanladı. Mann-Whitney testleri ve Spearman korelasyonu da dahil olmak üzere istatistiksel analiz yapıldı.

Bulgular: 50 videonun 45'i gerçek görüntüler içerirken, 5'i animasyondu. Fizyoterapistler en çok katkı sağlayan gruptu (%40), ve videoların %60'ı donuk omuzla ilgili genel bilgiler içermekteydi. Ortalama DISCERN ve JAMA puanları dikkate alındığında, videolar çoğunlukla kalite açısından zayıf olarak değerlendirildi. Doktor ve doktor olmayan kullanıcıların yükledikleri videolar arasında istatistiksel olarak anlamlı farklar bulunamadı. Videoları değerlendiren gözlemciler arasındaki ilişki mükemmeldi.

Sonuç: Donuk omuz hakkında bilgi arayan internet kullanıcıları, güvenilir içeriği ayırt etme konusunda zorluklarla karşılaşmaktadır. Sağlık profesyonelleri doğru bilgiler içeren videoları paylaşmalı ve hastaları güvenilir çevrimiçi kaynaklara yönlendirmelidir.

Anahtar Kelimeler: Donuk omuz, adeziv kapsülit, hasta eğitimi, bilgi, Youtube

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*Corresponding Author: Şafak Aydın Şimşek, MD: Ondokuz Mayis University Faculty of Medicine, Department of Orthopedics and Traumatology, 55139 Atakum, Samsun, Türkiye Phone: +903623121919 / mail: drsafakaydin@gmail.com

Orcid: 0000-0003-2250-8043

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Introduction

A frozen shoulder is thought to result from synovial inflammation and subsequent joint capsule fibrosis. It is characterized by discomfort and should decline the ability to move the shoulder [1]. The exact incidence and prevalence of frozen shoulder are not established; however, multiple authors have reported a general occurrence of 2-5% in the population, primarily affecting individuals aged between 40 and 60, with a higher prevalence in women. [2]. Long-term shoulder immobilization due to trauma and surgery, along with systemic diseases like diabetes, hyperthyroidism, hypothyroidism, cardiovascular disease, or Parkinson's disease, elevates the risk for certain patients [3]. Patients complain of limited movement on the affected side, pain and inability to sleep when a load is placed on the same side [4].

Engaging in online searches for health-related information has become commonplace among individuals. Findings from studies indicate that a substantial percentage, up to 79%, of Internet users in the United States are involved in researching health-related information [5]. Patients turn to the internet to learn more about medical conditions, medications, and treatments. Low-quality and untrustworthy information can be found in medical information sources on the general Internet and online social networks [6].

When reviewing the literature, it is concluded that the reliability of Youtube content on health-related topics needs to be questioned in many aspects. Frozen shoulder, which presents with sinovial inflammation and joint capsule fibrosis, reducing joint range of motion and affecting patient comfort, is an important condition encountered in Orthopedics and Traumatology practice. The approach of doctors and other healthcare professionals to frozen shoulder varies. When looking at videos on this topic on Youtube, it is possible to come across numerous contents uploaded by experts in various fields or individual accounts. However, the issue of patients accessing accurate and reliable information through Youtube content is debatable. This study aims to assess the credibility of videos posted on the YouTube sharing platform by evaluating Frozen Shoulder disease according to the Discern and Jama scoring system.

Materials and Methods

A search for "Frozen shoulder" was initiated by entering the term into the YouTube search bar (YouTube, www.youtube.com YouTube LLC, San Bruno, CA, USA) at 25/11/2023. The first 50 videos whose titles have the term ‘‘frozen shoulder’’ were evaluated. Exclusion criteria involved videos shorter than 30 seconds, repetitive content, advertisements, and those presented in languages other than English. The study's approach systematically categorizes videos into subgroups, considering factors like the type of image, uploaders, and content categories such as general information, non-surgical treatment, exercise training, and massage. Uploaders were categorized as physicians, chiropractors, physical therapists, and health and hospital channels. Important metrics were recorded, such as the number of views, the date of upload, the number of comments, the number of likes, the number of dislikes, and the duration of each video. The formula used to calculate the Video Power Index (VPI) values—which represent the popularity of the videos—was [(like count/dislike count + like count) x 100)] [7].

The DISCERN tool, designed by employees of Oxford University and the British Library, is valuable for assessing the quality of health-related videos on YouTube. The DISCERN tool utilizes a 5-point scale for scoring each of its 15 questions, contributing to total scores ranging from 15 to 75 points, indicating the information's quality. DISCERN’s questions have two sections. The DISCERN tool is structured with its first section (questions 1-8) focused on assessing the publication's reliability. The second section of the DISCERN tool, comprising questions 9 to 15, assesses the treatment options' relevance. The classification system for DISCERN scores is as follows: scores between 63 and 75 points are labeled as 'excellent', 51 to 62 as 'good', 39 to 50 as 'average', 28 to 38 as 'poor', and scores below 28 are considered 'very poor'. A higher score indicates a higher quality of information [8] (Table 1). The JAMA scoring system is a scale that includes four criteria—Authorship, Attribution, Disclosure, and Currency—assigning 1 point to

each, summing up to 4 points [9] (Table 2).

Table 1: Discern Scoring System

Section	Questions	No	Partly			Yes
Reliability of the publication	1.Explicit aims	1	2	3	4	5
	2.Aims achived	1	2	3	4	5
	3.Relevance to patients	1	2	3	4	5
	4.Source of information	1	2	3	4	5
	5.Currency(data) of information	1	2	3	4	5
	6.Bias and balance	1	2	3	4	5
	7.Additional sources of information	1	2	3	4	5
	8.Reference to areas of uncertainty	1	2	3	4	5
Quality of information on treatment choices	9.How treatment works	1	2	3	4	5
	10.Benefits of treatment	1	2	3	4	5
	11.Risk of treatment	1	2	3	4	5
	12.No treatment options	1	2	3	4	5
	13.Quality of life	1	2	3	4	5
	14.Other treatment options	1	2	3	4	5
	15.Shared decision making	1	2	3	4	5

Table 2: Jama Scoring System

Jama Scoring System		Rating	
Section		Yes	No
Authorship	Authors and contributors, their affiliations, and relevant credentials should be provided	1	0
Attiribution	References and sources for all content should be listed clearly, and all relevant copyright information should be noted	1	0
Disclosure	Website "ownership" should be prominently and fully disclosed, as should any sponsorship, advertising, underwriting, commercial funding arrangements or support, or potential conflicts of interest	1	0
Currency	Dates when content was posted and updated should be indicated	1	0

To determine the mean Daily view count, the total view count recorded by observers during video evaluation was divided by the days between the viewing date and the video's upload date on YouTube. The same group of observers watched each video simultaneously, independently recording the scores for JAMA (Journal of the American Medical Association) and DISCERN (Quality Criteria for Consumer Health Information). An average score was then calculated. (First observer's DISCERN score + second observer's DISCERN score) / 2 is the mean DISCERN score. The mean JAMA score equals the sum of the first and second observer's scores divided by two.

Approval for the study was granted by the Institutional Ethics Committee (decision no: B.30.2.ODM.0.20.08/447 dated:23.06.2022). The authors read the Helsinki Declaration and approved ethical obligations for the study.

Statistical Analysis

The study data underwent analysis using the SPSS 26.0 statistical package program, and results were expressed in numbers, percentages, mean ± standard deviation, median, minimum, and maximum values. Based on the normality test results, the Mann-Whitney non-parametric test was used to compare the mean DISCERN and JAMA scores between the physicians and non-physicians. The association between DISCERN and JAMA scores was evaluated using Spearman correlation analysis, which classified correlation coefficients as weak (r: 0-0.24), moderate (r: 0.25-0.49), strong (r: 0.50-0.74), and very strong (r: 0.75-1.0). Interobserver agreement was evaluated with Cronbach's α, where values <0.5 were deemed unacceptable, 0.5 ≤ α <0.6 as poor, 0.6 ≤ α <0.7 as acceptable, and 0.7 ≤ α <0.9 as excellent. Statistically significant differences were determined at $p < 0.05$.

Results

45 of 50 videos contained real images, and 5 videos were in animation form. The number of videos shared by a physician amounted to 8, whereas those shared by a physical therapist totaled 20. When video contents were analyzed, 30 videos were about general information (60%), and 12 videos were about exercise training (24%) (Table 3) (Figure 1).

Among the shared videos, the most extended video was 32 minutes and 44 seconds, while the shortest video was 30 seconds. The video

with the highest number of clicks was viewed 1,890,000 times, and the duration of the video was 25 minutes and 38 seconds. Looking at the date of sharing, the most recent post is from 1 month ago, and the oldest post was made in 2014. Video lengths, views, time since uploading, daily views, comments, likes, dislikes, and Video Power Index (VPI) values are all listed in Table 4. The distribution of video features by uploaders is displayed in Table 5.

Table 3: General features of the videos

General features of the videos		
	n	%
Image type		
Real	45	90.0
Animation	5	10.0
Uploaders		
Physician	8	16.0
Health channel	7	14.0
Chiropractor	5	10.0
Physical therapist	20	40.0
Fitness coach	3	6.0
Hospital channel	7	14.0
Video content		
General information	30	60.0
Non-Surgical treatment	3	6.0
Exercise training	12	24.0
Massage	5	10.0

Table 4: Parameters of videos

Variables	Mean±Standard Deviation	Median (Minimum-Maximum
Video length (minutes)	7.18±7.32	4.40(0.3-32.44)
View count	260280±405298	66223(1906-1890000)
Time since video upload(days)	1268±842	1116(31-3297)
View count (daily)	15745±75772	143.94(2.66-433256)
Comment count	180±346	61.5(0-2186)
Like count	4372±6459	1741(16-34585)
Dislike count	178±379	31.5(0-2300)
VPI (Video Power Index) (%)	95±5	97.04(79.07-100)

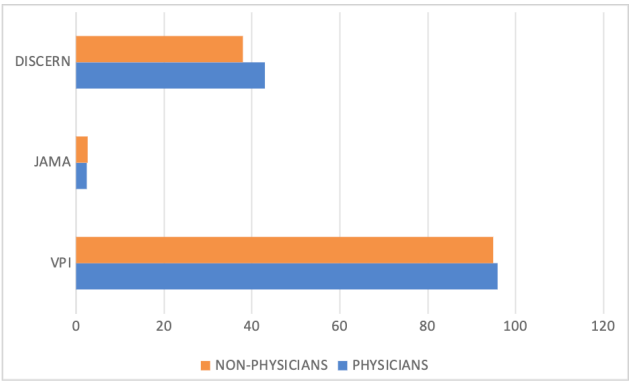
The potential differences between the physicians and non-physicians were evaluated by analyzing the values of the DISCERN, JAMA, and Video Power Index (VPI) assigned by the observers. There was no statistically significant difference found between the two groups for the average VPI, JAMA, and DISCERN values for videos that a doctor shared (p> 0.05).

Table 5: Distribution of the video features according to the uploaders

	Number of videos	Video Length (minutes)	Mean		
			Like	Dislike	Comment
Physician	8	7.74 ±2.89	3040 ±1494	33 ±15	83 ±29
Physical Therapist	20	2.05 ±0.48	978 ±758	89 ±66	51 ±42
Fitness Coach	3	1.61	4747 ±1289	156 ±60	202 ±53
Health Channel	7	11.24 ±3.90	5677 ±4827	127 ±95	321 ±310
Hospital Channel	7	4.91±3.66	8159 ±2273	401 ±99	204 ±88
Chiropractor	5	8.95±2.25	5654 ±2157	557 ±441	220± 109

Upon examination of DISCERN scores using Spearman correlation analysis, a highly robust and statistically significant correlation was observed (r: 0.921, p <0.001), indicating excellent agreement between the two observers (Cronbach α = 0.998). Similarly, the Spearman correlation analysis for JAMA scores revealed a strong and statistically significant correlation (r: 0.493, p <0.001), with an excellent level of agreement between the two observers (Cronbach α = 0.938). Both DISCERN and JAMA scores demonstrated high consistency and agreement between the evaluators.

Table 6: Comparison of DISCERN, JAMA and VPI values in non-physicians and physicians groups



The initial observer assigned a DISCERN score of 44.25±3.77 to the videos, while the second observer scored 43.50±3.56. Regarding JAMA scores, the

first observer awarded a score of 3±0.18, whereas the second observer's assessment yielded a score of 2.37±0.32. By looking at the mean DISCERN scores by two observers, it was discovered that the quality of the videos was very poor in 6% (n=3), poor in 46% (n=23), average in 32% (n=16), and good in 16% (n=8) (Figure 2).

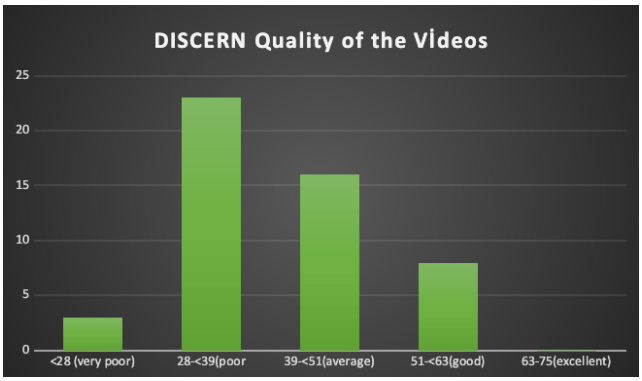


Figure 1: Distribution of the video publishers

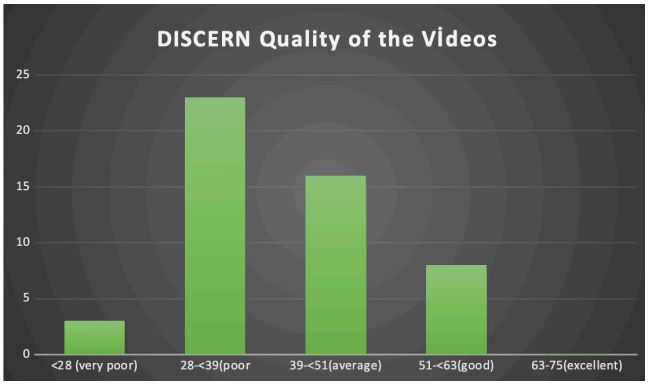


Figure 2: Distribution of quality of the videos according to the DISCERN scoring system

Discussion

This study highlights the challenge patients encounter in distinguishing between reliable and potentially misleading medical information on YouTube, particularly regarding frozen shoulder conditions. Frozen shoulders are a common problem in general orthopedic practice. Frozen shoulders affect 2.4 out of every 1000 person-years, or 2% of the general population [10]. When the patient has severe shoulder pain, which has been present for over a month, and stiffness of the shoulder joint, we could suspect a frozen shoulder [11]. Operative intervention, such as manipulation under anesthesia or arthroscopic capsular release, could be required in a small group of patients [12].

As of October 2023, there were 5.3 billion active internet users worldwide, which amounted to 65.7 percent of the global population, and 4.95 billion of these people were social media users [13]. Numerous patients—mostly younger men—use the Internet to look up orthopedic information in bulk. According to Burrus et al.'s research, 64.7% of patients who had access to the Internet did so specifically to look up orthopedic information [14]. The most popular website on the internet for finding information with videos is YouTube. Nonetheless, there has been discussion in the literature regarding the validity and accuracy of the health-related information found online [15]. The orthopedic videos available on YouTube often don't need an editorial process, contributing to concerns about the information's reliability. Therefore, the accessibility of reliable and accurate information about their medical conditions remains limited for Internet users. Understanding and evaluating YouTube resources is paramount for orthopedic surgeons, as it equips them with the necessary information to educate and assist patients in navigating the complexities of their disease management.

Among the 50 videos analyzed in our study, a notable 10% (n=5) were animated, while the majority, constituting 90% (n=45), featured real images. The animated videos were sourced from various contributors, including a physician (n=1), physical therapists (n=3), and a health channel (n=1). Non-physician contributors uploaded most videos under examination (n=42, 84%). The distribution of the 50 videos revealed that physical therapists were the most frequent contributors, sharing 40% of the content, followed by health channels (14%), hospital channels (14%), chiropractors (10%), and fitness coaches (6%). Physicians uploaded eight videos. In a separate study focussing on rotator cuff tears and involving 50 videos, 72% were shared by non-physicians, highlighting the substantial influence of non-medical sources in the dissemination of this specific orthopedic condition. Additionally, 16% of the videos were animated, with health channels being a common source for such animations [7]. Consistent with the literature, the mean video length in this study was identified as 7.18 minutes, aligning with the range observed in earlier research, where mean video durations were reported to fall between 6.59

and 7.56 minutes. [7,16].

Diverse scoring systems, as highlighted in the literature, serve the purpose of evaluating the quality and accuracy of online videos (17). The DISCERN and JAMA scoring systems, commonly featured in the literature, were chosen for our study to maintain comparability with established research practices in evaluating video content. The mean Video Power Index was 95±5 %. The quality of the videos was mainly in the 'poor' category. The values for the Video Power Index (VPI), JAMA, and DISCERN that observers assigned were compared between the physician and non-physician groups to evaluate any potential variations. The average DISCERN, JAMA, and VPI values in the videos that a doctor shared did not show a statistically significant difference between the two groups ($p>0.05$). Previous studies have demonstrated a disparity, highlighting that medical information shared by physicians tends to be superior to that provided by non-physicians [18]. This comparison raises the possibility that doctors' videos aren't of high enough quality.

The most common video content was about general information (n=30, 60%). Of the 50 videos evaluated, 3 (6%) included non-surgical treatment, 12 (24%) included exercise training, and 5 (10%) were about massage. In another study about rotator cuff tears, non-surgical information was featured in the content of forty-three of the evaluated videos [7]. This result may be thought to the patients who want to understand the definition of a frozen shoulder and which situations indicate a frozen shoulder. Health professionals should upload accurate and reliable videos and show the correct sources of the information. This way, patients can find the correct way on social media platforms.

This study has some limitations. Initially, our evaluation was limited to the first 50 videos with titles containing 'frozen shoulder', preventing us from analyzing the entirety of Youtube videos on this subject. Another limiting factor of the study is that it only focused on videos on the YouTube platform, more detailed studies covering video content on Google can be planned. We could not evaluate the association between comments, like count, dislike counts, and the video's length, view count, and quality. DISCERN and JAMA scoring systems, which were common in the literature, were used to evaluate the quality of the videos.

Conclusion

This study highlights patients' difficulty distinguishing between trustworthy and potentially misleading medical information on YouTube, particularly regarding frozen shoulders. Significantly, the patients want to know the frozen shoulder clinic features. We believe that social media platforms become much more important to patients' behavior about health, and health professionals should use the Internet to guide patients to accurate medical information. Further studies about orthopedics and other medical fields will contribute to the quality and reliability of health-related video content.

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ORCID and Author contribution: **T.C. (0000-0003-2363-0198):** Concept and Design, Writing, Critical Review. Final Approval. **Ş.A.Ş. (0000-0003-2250-8043):** Data Collection, Interpretation of Results, Literature Search, Writing. **A.E. (0000-0003-3427-8337):** Data Collection, Interpretation of Results, Literature Search. **H.S.C. (0000-0003-2965-3112):** Writing, Critical Review. Final Approval. **A.P. (0000-0001-7473-8364):** Literature Search, Critical Review. Final Approval

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Evaluation of Peripheral Inflammatory Activity in Different Types of Dementia

Farklı Demans Tiplerinde Periferik İnflamatuar Aktivitenin Değerlendirilmesi

Esra Erkoç Ataoğlu[1*]

1.Department of Neurology, Faculty of Medicine, Gazi University, Türkiye

ABSTRACT

Aim: Alzheimer's disease (AD) is a chronic neurodegenerative disease characterized by pathophysiological processes involving neuroinflammation, neurodegeneration, and synaptic dysfunction. Vascular dementia (VaD) stands as the second most prevalent form among all dementia types, sharing common pathophysiological mechanisms with AD, such as vascular oxidative stress and chronic inflammation. The neutrophil-to-lymphocyte ratio (NLR) is considered a simple, noninvasive, and widely available clinical marker of inflammation. The aim of this study is to investigate the potential differences between these two different types of dementia in terms of NLR values.

Materials and Methods: The data of patients diagnosed with AD or VaD and healthy controls who applied to a University Hospital Neurology outpatient clinic were retrospectively examined, and the groups were analyzed with statistical methods in terms of NLR levels.

Results: A total of 39 AD, 32 VaD, and 30 healthy controls were enrolled in the study. Hemogram analyses revealed significantly elevated NLR values in both the AD and VaD groups compared to the healthy control group ($p = .001$, $p = .001$, respectively). AD and VaD groups demonstrated no significant difference in NLR ($p = .787$). Additionally, as a result of regression analyses, it was determined that age and NLR were independent variables associated with the presence of dementia.

Conclusions: NLR values are at higher levels in AD and VaD patient groups compared to healthy controls. Our results support the role of peripheral inflammation in the pathogenesis of VaD, as in AD. Additional studies are needed on potential inflammatory biomarkers of VaD.

Keywords: Alzheimer's disease, Vascular dementia, NLR, Neuroinflammation

ÖZ

Amaç: Alzheimer hastalığı (AH), nöroinflamasyon, nörodejenerasyon ve sinaptik işlev bozukluğu gibi karmaşık patofizyolojik süreçlerle karakterize kronik bir nörodejeneratif hastalıktır. Vasküler demans (VaD), tüm demans türleri arasında ikinci en yaygın form olup, vasküler oksidatif stres ve kronik inflamasyon gibi AH ile ortak patofizyolojik mekanizmalara sahiptir. Nötrofil-lenfosit oranı (NLR), inflamasyonun basit, invaziv olmayan ve yaygın olarak kullanılabilen bir klinik belirleyicisi olarak kabul edilmektedir. Bu çalışmanın amacı, NLR değerleri açısından, bu iki farklı demans tipi arasındaki potansiyel farkları araştırmaktır.

Hastalar ve Yöntem: Bir Üniversite Hastanesi Nöroloji polikliniğine başvuran, AH veya VaD tanısı alan hastaların ve sağlıklı kontrollerin verileri retrospektif olarak incelenerek, gruplar NLR düzeyleri açısından istatistiksel yöntemlerle analiz edilmiştir.

Bulgular: Çalışmaya toplamda 39 AH hastası, 32 VaD hastası ve 30 sağlıklı kontrol dahil edildi. Hemogram analizleri, AH ve VaD gruplarında NLR değerlerinin sağlıklı kontrol grubuna kıyasla anlamlı bir şekilde yüksek olduğunu ortaya koydu (sırasıyla $p = .001$, $p = .001$). AH ve VaD grupları arasında NLR'de anlamlı bir fark saptanmadı ($p = .787$). Ayrıca, regresyon analizleri sonucunda, yaş ve NLR'nin demans varlığı ile ilişkili bağımsız değişkenler olduğu belirlendi.

Sonuç: NLR değerleri, AH ve VaD hasta gruplarında sağlıklı kontrollere göre yüksek seviyelerdedir. Sonuçlarımız, VaD patogenezinde de, AH'de olduğu gibi periferik inflamasyonun rolünü desteklemektedir. VaD'nin potansiyel inflamatuar biyobelirteçleri konusunda ek çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Alzheimer Hastalığı, Vasküler Demans, NLR, Nöroinflamasyon

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*Corresponding Author: Esra Erkoç Ataoğlu, MD, Gazi University, Faculty of Medicine, Department of Neurology, Beşevler/Ankara/Türkiye, Phone: +905327350458 / mail: esraerkoc@hotmail.com

Orcid: 0000-0001-5465-6089

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by impairment in cognitive functions, especially memory, and deterioration in daily living activities, as well as neuropsychiatric symptoms and behavioral changes. Amyloid plaques and neurofibrillary tangles are pathologic hallmarks of the disease [1, 2]. There are certain complex pathophysiological processes involving neuroinflammation, neurodegeneration, and synaptic dysfunction in AD [1]. Activated astrocytes and microglia have an important role in chronic neuroinflammation that facilitates neuronal death and the accumulation of intracellular beta-amyloid plaques and intraneuronal neurofibrillary tangles, resulting in both the onset and progression of the disease [2-6]. In addition, it seems that inflammation reaches beyond the confines of the central nervous system (CNS), as various indicators of systemic inflammation have been observed to elevate throughout the progression of the disease in AD [3, 7-9].

Vascular dementia (VaD) emerges as the second most widespread manifestation among all dementia types, manifesting through cognitive impairment, functional deterioration, behavioral disturbances, and neurological symptoms arising as sequelae to cerebrovascular disease (CVD). There are shared pathophysiological mechanisms with AD including vascular oxidative stress and chronic inflammation, serving as pivotal pathogenic elements contributing to neurovascular dysfunction [10-13].

Circulating peripheral cells such as leukocytes, lymphocytes, and neutrophils are widely used in the literature as markers of systemic inflammation [8, 9, 14, 15]. The Neutrophil-to-Lymphocyte Ratio (NLR), calculated by dividing the neutrophil count by the number of lymphocytes in the complete blood count, is recognized as one of the simple, non-invasive, cost-effective, and widely available clinical markers of peripheral inflammation. It combines information from two leukocyte subtypes and eliminates the disadvantages of absolute leukocyte values, which are affected by factors such as infection and dehydration. NLR has demonstrated associations with a spectrum of health conditions, encompassing cerebrovascular and cardiovascular diseases, Diabetes Mellitus, Hypertension, as well as various malignancies [5, 14, 16]. Furthermore, multiple studies have indicated an elevation in NLR values among individuals with AD when compared to the general population. [4, 5, 8, 15, 17, 18]. Moreover, elevated NLR level was observed in the Mild Cognitive Impairment (MCI) group in comparison to the healthy control cohort [5, 8, 19]. To the best of our knowledge, NLR, as an inflammatory marker has not been comprehensively examined in the context of vascular dementia. In a recent study, NLR levels were examined in AD and VaD types, the NLR level was found to be significantly higher in AD patients than the VaD patients [20]. It is unknown whether NLR levels in the VaD group differ from healthy individuals.

This study aims to evaluate the potential differences and diagnostic use of Neutrophil-Lymphocyte Ratio (NLR), as a well-defined inflammatory marker, in Alzheimer's disease (AD), vascular dementia (VaD), and healthy individuals.

Material-Method

We retrospectively collected the data of patients aged >65 years diagnosed with AD or VaD, and healthy controls, who had been admitted to Gazi University Faculty of Medicine, Department of Neurology outpatient clinic between January 2022 and June 2023.

Individuals with a confirmed diagnosis of probable AD, following the National Institute on Aging and Alzheimer’s Association (NIA-AA) criteria, and those diagnosed with VaD based on the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria following thorough clinical assessment and subsequent diagnostic evaluation, were included for further analysis in this study [12, 21].

Patients with diagnoses of malignancy, renal, hepatic, or chronic heart failure, coronary artery disease, connective tissue disease, hematological disease, infectious diseases, endocrine disorders, or autoimmune conditions that could potentially influence routine blood parameters were excluded from the study.

The control group in our study consisted of healthy volunteers aged over 65 years who did not have memory complaints, any comorbidities that may affect routine blood parameters, whose cognitive tests were normal, who were examined in our outpatient clinic for other reasons, and who were given blood samples.

We retrospectively collected all demographic, clinical, neuroimaging, and laboratory data from the hospital database system. Age, gender, education, disease duration, results of clinical and neuropsychological examinations, and the scores of the Mini-Mental State Examination (MMSE) test were recorded for each patient.

Complete blood count data studied from samples taken following overnight fasting routinely collected into EDTA tubes and then subjected to automated hematological analysis (Unicel® DxH800 automatic hematology analyzer) were recorded. Neutrophil and Lymphocyte counts and NLR, were analyzed in AD, VaD, and healthy control groups.

This retrospective study adhered to the ethical principles outlined in the Helsinki Declaration, and the study protocol received approval from the Ethics Committee of Gazi University Faculty of Medicine (2023/878).

Statistical analyses

The statistical analysis was carried out using the IBM SPSS 20 package program. The normality of numeric data was assessed using the Shapiro-Wilk test and presented as mean ± SD or median (min-max) where appropriate. Categorical variables were expressed as percentages. For pairwise comparisons, the Student's t-test or Mann-Whitney U test was employed based on the normality of the data. In cases where there were more than two groups, One-Way ANOVA or Kruskal-Wallis variance analysis was applied. Categorical variables underwent evaluation through the Chi-Square test. Simple correlations were performed using the Spearman test. To identify independent associates of dementia presence, a logistic regression model was employed. A two-tailed p-value of <0.05 was considered statistically significant.

Results

In total, 39 AD patients (17 men; mean age, 72.41 ±1.31 years), 32 VaD patients (17 men; mean age, 77.56 ±1.48 years), and 30 healthy controls (15 men; mean age, 68.53±2.10 years) were included in our study. The gender distribution and education level were similar among the three study groups; but the mean age was older among patients with VaD when compared to AD and healthy control groups (p=.037 and p=.001, respectively). There was no difference in age between AD and HC groups (p=.665).

Demographic characteristics and laboratory parameters of the study population are presented in Table 1.

Table -1. Baseline characteristics and hemogram parameters of the study population

	AD	VaD	HC	P
Age [years (mean±SD)]	72.41 ±1.31	77.56 ±1.48[a,b]	68.53±2.10	.001 *
Sex (F% vs M%)	56% vs 44%	47% vs 53%	%50 vs %50	.713
Education (<=8 years vs > 8 years)	51% vs 49%	66% vs 34%	%60 vs %40	.465
MMSE score	16.92 ± .61	17.53 ±.75	28.40±.27[c,d]	.000*
WBC (10 9/L)	7.23 ± .33	7.46 ±.31	7.00±.33	.654
NEU (10 9/L)	4.52 ± .26	4.75 ±.26	3.94±.24	.138
LYM (10 9/L)	1.86 ± .11	1.95 ±.12	2.23 ± .10	.07
NLR (Neutrophil/ Lymphocyte Ratio)	2.81±.28	2.71±.22	1.81±.11[e,f]	.001*

*p < 0.05

a p=.001 (VaD vs HC), b p=.037 (VaD vs AD), c p= .001 (AD vs HC), d p= .001 (VaD vs HC),

e p=.001 (AD vs HC), f p =.001 (VaD vs HC)

Regarding the patients with dementia, MMSE scores were similar in both AD and VaD groups (16.92 ± .61 for AD vs 17.53 ±.75 for VaD, p=.624); however, disease duration was longer in patients with AD (3.51±.13 years for AD, 3.09±.16 years for VaD, p=.022).

In Hemogram analyses, WBC, NEU, and LYM counts were similar among the three study groups (p= .654, p=.139, p=.07, respectively). Nevertheless, the NLR value demonstrated a significant difference between patients and controls, which was 2.81±.28 for AD patients, 2.71±.22 for VaD patients, and 1.81±.11 for

healthy controls (p=.001). Pairwise comparisons revealed no difference between patients with AD and VaD in terms of NLR (p=.787).

No significant correlation was demonstrated between NLR and age, regarding the whole study population or patients with dementia (p=0.087 and p=0.170 respectively).

Both univariate and multivariate regression analyses showed that age and NLR were independently associated with the presence of dementia (Table 2).

Table-2 Regression analysis for the independent associates of dementia presence

	Univariate analysis			Multivariate analysis		
	Exp (B)	(%95 CI)	p	Exp (B)	(%95 CI)	p
Age	1.063	1.012-1.117	**0.015***	1.056	1.000-1.115	**0.048***
Sex	1.316	0.501-3.457	0.577	1.015	0.350-2.941	0.978
Education	0.433	0.164-1.142	0.091	0.721	0.246-2.111	0.551
NLR	3.120	1.504-6.470	**0.002***	2.994	1.383-6.478	**0.005***

Discussion

In our current investigation, it emerged that individuals diagnosed with AD or VaD exhibited heightened NLR levels in comparison to the healthy control group. There was no significant difference in NLR levels between the AD and VaD patient groups. Moreover, our findings highlighted the predictive capacity of NLR in indicating the presence of AD or VaD.

Our observations concerning AD align with a multitude of studies indicating elevated NLR levels in AD patients compared to healthy controls. This consistency lends support to the significant involvement of chronic inflammation in the pathogenesis of AD [4, 5, 7, 9, 14, 17, 18]. Also, our study reflected the importance of NLR as a peripheral inflammatory marker in the VaD group as well as in the AD group.

Activation of inflammatory markers in the peripheral circulation triggered by neuroinflammation has been the subject of much AD research. NLR is one of the most frequently studied peripheral inflammatory markers in the AD literature [5, 15, 17, 18]. First, Kuyumcu et. al found that the patients with AD have elevated NLR in comparison with healthy controls and NLR was strongly predictive for diagnosis of AD and the association between NLR-AD was independent of well-known confounders like age, gender, etc. [17]. The following studies about NLR showed similar results in AD and MCI groups [5, 8, 15, 18, 19, 22]. Similarly, our results demonstrated an independent association between NLR and the presence of dementia.

Neutrophils, considered pivotal inflammatory cells, may increase in numbers stimulated by certain inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a) and interleukin-9 (IL-9), both implicated in the pathogenesis of AD [9, 23]. Elevated neutrophil counts, prompt T-cell activation and release of TNF-a. The chronic release of TNF-a by microglia is implicated in the accumulation of amyloid-beta (Ab) and phosphorylated tau (p-tau) [5, 25]. Furthermore, the activation of neutrophils plays a contributory role in the worsening of neurodegenerative diseases by causing damage to the blood–brain barrier (BBB). The increased migration of peripheral neutrophils and lymphocytes into the central nervous system, coupled with heightened neutrophil production in circulation, results in a substantial elevation of the peripheral NLR in patients diagnosed with AD and MCI [5, 23, 25-27].

Vascular oxidative stress and inflammation stand out as pivotal pathogenic factors contributing to neurovascular dysfunction and underlie many deleterious effects observed in VaD [10]. Inflammation serves as a central process linking various cardiovascular risk factors to both vascular and neuronal damage. Plasma levels of inflammatory proteins, including α1-antichymotrypsin, C-reactive protein, and IL-6, have been noted to rise years before the onset of VaD [25, 28]. Platelet and related inflammatory markers, such as Mean Platelet Volume (MPV) and Platelet-to-Lymphocyte Ratio (PLR), have been evaluated in several VaD studies. However, research on the role of NLR as an inflammatory marker in VaD cases remains limited. A recent study by Bulut et al. assessed NLR in VaD, revealing significantly higher levels in the AD group compared to the VaD group [20]. In contrast, our study found no significant difference between VaD and AD patients in terms of NLR, with both groups exhibiting higher NLR values than healthy controls. To the best of our knowledge, this is the first study that evaluated NLR in the VaD group

and healthy controls and showed that NLR values are significantly elevated in VaD compared to healthy controls. Our findings lend support to the involvement of peripheral inflammation in the pathogenesis of VaD, similar to AD. Prior studies have proposed that the elevated NLR observed in Alzheimer's disease might be a consequence of aging [15]. Based on this, our findings that the higher mean age in the VaD group compared to the controls may be thought as another potential reason for the higher NLR levels in VaD. However, our analyses did not detect any correlation between age and NLR levels, both in assessments involving all participants and within the dementia patient groups. Consequently, the elevated NLR levels observed in the VaD group are more likely attributable to the role of inflammation in the pathogenesis of VaD.

Limitations

Several limitations exist in the current study. Firstly, the relatively small sample size may hinder the generalizability of the findings. Secondly, the retrospective design of the study precludes the availability of follow-up data, thereby limiting our ability to predict subsequent clinical implications based on the observed results. Another limitation of our study is that the traditional inflammatory markers like CRP, TNF alpha, and interleukins, have not been assessed. However, the main objective of the current study was the prediction of dementia through a simple and inexpensive method like a routine hemogram.

Conclusion

In summary, our study concludes that individuals with Vascular Dementia (VaD) exhibit elevated Neutrophil-to-Lymphocyte Ratio (NLR) levels, highlighting the involvement of inflammatory pathophysiology, akin to Alzheimer's disease (AD). Future investigations with larger populations and longitudinal follow-up are essential to validate our findings and explore the pathophysiological and clinical significance of alterations in peripheral blood cells for the management of VaD.

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Birth Order and Number of Siblings in Attention Deficit Hyperactivity Disorder: A Case Control Study

Dikkat Eksikliği ve Hiperaktivite Bozukluğu'nda Doğum Sırası ve Kardeş Sayısı: Olgu Kontrol Çalışması

Orhan Kocaman[1*], Tayfun Kara[1], Pınar Aydoğan Avşar[2], Tacettin Kuru[3]

1.Department of Child and Adolescent Psychiatry, Alanya Alaaddin Keykubat University, Faculty of Medicine, Antalya, Türkiye
2.Department of Child and Adolescent Psychiatry, Alanya Training and Research Hospital, Antalya, Türkiye
3.Department of Psychiatry, Alanya Training and Research Hospital, Antalya, Türkiye

ABSTRACT

Aim: Studies addressing the etiology of Attention Deficit Hyperactivity Disorder (ADHD) in recent years have focused on family and birth-related factors.This study aimed to examine the relationship between Attention Deficit Hyperactivity Disorder (ADHD) and birth order and number of siblings.
Method: A total of 239 participants, 135 children diagnosed with ADHD and 104 healthy children, were included in the study. All participants were evaluated through DSM-5-based psychiatric examinations, and their sociodemographic data forms were obtained. Conners' Parent Rating Scale-Revised Short form (CPRS-RS) was also applied to the case group in order to determine the severity of ADHD symptoms. The findings were then compared using statistical methods.
Results: No significant difference was observed between the individuals with ADHD and the healthy controls in terms of birth order or number of siblings (p= 0.252 and p= 0.222, respectively). A significant positive correlation was determined in the ADHD group between birth order and hyperactivity and oppositional subscales (r= 0.212, p= 0.022 and r= 0.231, p= 0.012, respectively). A significant positive correlation was also determined in the ADHD group between number of siblings and the oppositional subscale (r= 0.237, p= 0.009).
Conclusions:In our study, no significant difference was observed between the ADHD and control groups in terms of birth order or number of siblings.It was observed that hyperactivity and defiance symptoms increased as birth order increased in children diagnosed with ADHD. Oppositional findings also increased in line with the number of siblings.We think that these findings should be taken into consideration in future research on ADHD.

Keywords: Attention-deficit hyperactivity disorder, birth order, number of siblings

ÖZ

Amaç: Son yıllarda Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) etyolojisine yönelik çalışmalarda aile ve doğuma ilişkin etkenlere odaklanılmıştır. Bu çalışmada Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) ile doğum sırası ve kardeş sayısı arasındaki ilişkinin incelenmesi amaçlanmıştır.
Yöntem: Çalışmaya DEHB tanısına sahip 135 çocuk ile 104 sağlıklı çocuk olmak üzere toplam 239 katılımcı alınmıştır. Tüm katılımcılar DSM-5 temelli psikiyatrik muayene ile değerlendirilmiş ve sosyodemografik veri formları elde edilmiştir. Olgu grubuna ilave olarak DEHB belirti şiddetini değerlendirmek için Conners Anababa Dereceleme Ölçeği-Yenilenmiş Kısa Formu uygulanmıştır. Elde edilen bulgular istatistiksel yöntemler ile karşılaştırılmıştır.
Bulgular: DEHB olan bireyler ile sağlıklı kontroller arasında doğum sırası ve kardeş sayısı açısından anlamlı farklılık saptanmamıştır (sırasıyla p=0,252/p=0,222). DEHB'li grupta doğum sırası ile hiperaktivite ve karşı gelme alt ölçekleri arasında anlamlı düzeyde pozitif korelasyon saptanmıştır (sırasıyla r=0.212, p=0,022/ r=0,231, p=0,012). DEHB li grupta kardeş sayısı ile karşı gelme alt ölçeği arasında anlamlı düzeyde pozitif korelasyon saptanmıştır (r=0,237, p=0,009).
Sonuç: Çalışmamızda DEHB ve kontrol grubu arasında doğum sırası ve kardeş sayısı açısından anlamlı fark saptanmadı. DEHB tanılı çocuklarda doğum sırası arttıkça hiperaktivite ve karşı gelme bulgularının arttığı görüldü. Aynı zamanda kardeş sayısı arttıkça karşıt gelme bulgularının arttığı görüldü. Bu bulguların gelecekteki DEHB'ye yönelik araştırmalarda dikkate alınması gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, doğum sırası, kardeş sayısı

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*Corresponding Author: Orhan Kocaman, MD. Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Child and Adolescent Psychiatry, Oba Mah. Fidanlık Cad. Alanya/ Antalya/ Türkiye. Phone:+905324882207 / mail: dr_orhankocaman@hotmail.com

ORCID: 0000-0002-7504-5604

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most commonly seen neurodevelopmental disorders in childhood and adolescence. It is characterized by hyperactivity, impulsivity, and attention deficit symptoms [1]. The prevalence in childhood and adolescence ranges between 2% and 7% [2] and a visible increase has been experienced in the number of children diagnosed with ADHD in recent years [3]. Genetic, epigenetic, and environmental risk factors are thought to play a role in the etiology. Studies of the etiology of ADHD initially concentrated on genetic factors, although the focus in recent years has been on environmental risk factors [4]. Research into the etiology of ADHD has suggested that environmental risk factors are responsible for 20-30% of phenotypic variability in ADHD symptoms [5].

Birth order is defined as the order in which a child is born among its siblings. It plays an important role in the child's psychological development and also affect the development of an individual's psychopathology [6]. Relationships between birth order and psychopathology have therefore attracted the interest of several researchers [7]. It has been suggested that birth order plays an important role in the etiology of ADHD as one of the familial factors. The numbers of studies investigating the relationship between birth order and ADHD are limited. Differing results have also been reported. While some research has observed an association between birth order and ADHD, other studies have found no relationship [8–10]. There are various hypotheses concerning the effect of birth order on the development of psychiatric diseases. One of these is that in pregnancies involving maternal-fetal incompatibility, early pregnancies render the mother immunologically more sensitive to subsequent pregnancies. This situation, which depends on the order or pregnancy rather than on the age of the mother is capable of triggering immunological process involved in the development of psychiatric disorders. Studies have suggested that this immunological sensitivity plays a role in the development of psychiatric disorders [11]. Another hypothesis is that the disease risk may be associated with parental ages, and that the ages of the parents may rise indirectly in line with birth order. Advanced parental age may contribute to the development of psychiatric disorders by triggering de novo mutations [12].

Having siblings affects the individual's mental development. First, middle, or later-born children may exhibit different developmental and personality characteristics to children with no siblings. Living in families with large numbers of siblings, and being the first or last child, has been proposed as a potential risk factor in terms of neurodevelopmental disorders [6]. It has been suggested that possession of a large number of siblings may reduce the adverse effects of birth order in some diseases. Sibling numbers as well as birth order should therefore be considered in studies investigating the relationship between ADHD and familial factors [13].

Few studies have examined the relationship between ADHD and birth order and number of siblings, and their findings are inconsistent. The purpose of this study was therefore to examine the association between the severity of ADHD symptoms and birth order and number of siblings.

Method

Sampling and Application

This study was performed with 239 children and adolescents, 135 diagnosed with ADHD and 104 healthy volunteers. The study sample was obtained from a children's hospital child and adolescent psychiatry outpatient clinic. All participating adolescents underwent Diagnostic and Statistical Manual of Mental Disorders-5 (DSM 5 TR) based psychiatric evaluations, because of the exclusion of another psychiatric disease. These were conducted by experienced child and adolescent mental health and diseases specialists. The Conners Parent Rating Scale-Revised Short form (CPRS-RS) was complete to screen the severity of the children's ADHD symptoms. Non-biological mothers and fathers and individuals lacking the cognitive capacity required to read the forms and complete the scales were excluded. Twenty participants were excluded from the study (eleven due to comorbid psychiatric disorder and nine for incomplete filling of the forms), and study was performed with 135 participants. The control group was composed of individuals between the ages of

6-18 who had no physical disease or psychiatric disease according to DSM-5. An information form consisting of structured multiple-choice questions prepared by psychiatrists was used to determine the sociodemographic and clinical characteristics of all participants. Written and verbal consent was obtained from the families of all the participating. Ethical approval was granted by the Alanya Alaaddin Keykubat University clinical research ethical committee, Turkey (decision 17-01 dated 22/11/2023).

Tools

Sociodemographic Information Form: This investigated sociodemographic characteristics including name, surname, age, sex, education, number of siblings, and birth order.

Conners Parent Rating Scale-Revised Short Form (CPRS-RS): This form was developed by Conners in order to evaluate behaviors during childhood. It was produced by selecting the items with the highest factor loading following exploratory factor analysis applied to the data collected by Conners for the renewed long forms [14]. The CPRS-RS consists of 27 items in three subscales (Oppositional -O, Cognitive Problems/ Inattention-CP-I, and Hyperactivity-H) and one assistant scale (ADHD Index- ADHD-I). Each item is scored on a four-point scale from 0 to 3; Not true at all (very rarely), 0; somewhat true (sometimes), 1; quite true (frequently, 2; very true (very frequently), 3. Higher scores indicate greater possession of problems defined in the CPRS-RS. The validity and reliability of the Turkish-language version were established by Kaner [15].

Statistical Analysis

The study results were calculated as mean pus standard deviation for continuous variables and as percentage values for categorical variables. Deviation from normal for continuous variables was examined using skewness and kurtosis values. Values within a ± 1.5 for skewness and kurtosis were regarded as indicating normal distribution [16]. Differences in continuous variables measured between the control and case groups were evaluated using the independent samples t test. Comparison of the case and control groups in terms of categorical variables was performed using the chi-square and Fisher's exact tests. Relationships between variables were examined using Pearson coefficients. p values <0.05 were regarded as significant. Statistical analyses were performed on SPSS version 27 software.

Results

The study was conducted with 239 volunteers, 135 (56.5%) consisting of individuals diagnosed with ADHD. The participants' mean age was 9.81 years (SD = 2.28), and 164 (68.6%) were girls.

No significant differences were determined between the case and control groups in terms of age (t (236) = 690, p = 0.491) or gender (X2 (1, N=238) = 3.540, p = 0.060). No significant differences were also observed for the case and control groups in terms of birth order (p = 0.222) or number of siblings (X2 (3, N=236) = 4.093, p = 0,252) (Table 1).

Table 1: A comparison of the case and control groups

		Case (135)	Control (104)	t/X2	p
Age	(Mean ±SD)	9.90 ± 2.65	9.70±1.69	0.690	0.491
Sex (female)	(N. %)	99 (73.9%)	65(62.7%)	3.540	0.060
Number of siblingsa	1	20 (15.2%)	19 (18.3%)		
	2	76 (57.6%)	63 (60.6%)		
	3	26 (19.7%)	20 (19.2%)		
	4	10 (7.6%)	2 (1.9%)	4.093	0.252
Birth orderb	1	74 (56.5%)	56 (53.8%)		
	2	36 (27.5%)	39 (37.5%)		
	3	18 (13.7%)	8 (7.7%)		
		3(2.3%)	1 (1%)	4.297	0.222

The Independent Samples t Test, achi-square test, b Fisher's exact test. p<0.05 results shown in bold.

Table 2 shows the ADHD subscales in the case group according to the descriptive statistic results. All the subscales were found to be normally distributed (skewness and kurtosis values at a range of ± 1.5).

Pearson's product-moment correlation coefficients were calculated to determine relationships

between the ADHD subscales and number of siblings and birth order. A significant correlation was observed between number of siblings and the oppositional subscale (r = 0.237, p = 0.009). Birth order was significantly positively correlated with both the ADHD oppositional (r = 0.231, p = 0.012) and hyperactivity (r = 0.212, p = 0.022) subscales. The ADHD-I subscales exhibited no significant correlation with number of siblings (r = 0.182, p = 0.061) or birth order (r= 0.124, p = 0.204). Similarly, the cognitive problems/Inattention subscale exhibited no correlation with number of siblings (r = 0.081, p = 0.389) or birth order (r=0.060, p = 0.529) (Table 3).

Table 2: Descriptive Statistics

	Mean±Standard Deviation	Min-Max	Skewness	Kurtosis
Age	9.89 ± 2.65	6-17	0.38	-0.71
ADHD-I	22.10 ± 7.22	2-35	-0.47	-0.15
O	6.57 ± 3.50	0-12	-0.08	-1.10
CP/I	11.57 ± 4.45	0-18	-0.51	-0.45
HA	8.38 ± 5.13	0-18	0.17	-1.03

O: Oppositional, CP/I: Cognitive problems/Inattention, H: Hyperactivity. ADHD-I: ADHD-Index

		Number of siblings	Birth order
ADHD-I	r	0.182	0.124
	p	0.061	0.204
O	r	0.237	0.231
	p	0.009	0.012
CP/I	r	0.081	0.060
	p	0.389	0.529
HA	r	0.177	0.212
		0.057	0.022

r: Pearson's product-moment correlation coefficient. Statistically significant results shown in bold. O: Oppositional, CP/I: Cognitive problems/Inattention, H: Hyperactivity. p<0.05 results shown in bold.

Discussion

This study examined the relationship between ADHD and birth order and number of siblings. Statistical analysis revealed no significant difference between the case and control groups in terms of either variable. A significant correlation was observed between birth order and the hyperactivity and oppositional subscales in the children with ADHD. A significant correlation was also observed between number of siblings and the oppositional subscale in those children.

Familial and birth-related factors play a role in the etiology of ADHD. While the effect of each of these factors is small, they still contribute to the emergence of ADHD, particularly in individuals with genetic susceptibility [17]. Research investigation the association between ADHD and birth order has generally been conducted with large samples, but without control groups, children with ADHD being compared among themselves [8,13,18]. Studies involving a control group have found no association between ADHD and birth order [19,20]. Similarly in the present study, no difference was observed between the children with ADHD and the healthy controls in terms of birth order. We think that the use of different methodologies in research examining the relationship between ADHD and birth order, and the different sample size, may lead to variable results.

Impairments of parent-child relationships and familial functions are observed in the families of children diagnosed with ADHD. In particular, young children with ADHD experience greater conflict with parents than older children [21]. One study to date has examined the relationship between the severity of ADHD symptoms and birth order, but no association was determined [19]. In the present study, positive correlations were observed between birth order in the children with ADHD and the hyperactivity and oppositional subscale scores. The number of siblings increases indirectly in line with the birth order, and this finding of the present research may be attributable to the parents devoting less time to each child and experiencing difficulties in setting limits.

Research into the effect of the number of siblings on a child's mental health has shown that the presence of older or younger siblings have different impacts [22]. Studies addressing the relationship between number of siblings and ADHD have reported inconsistent findings. Some studies have reported fewer siblings in individuals with ADHD [19], while others have found no association between ADHD and sibling number [23]. Similarly in the present study, no significant difference was found between the children with ADHD and the healthy controls in terms of numbers of siblings. Being the first child is one of the predictive factors for ADHD [8] and it has been suggested that the difficult aspect of having a child with ADHD may

affect the decision to become pregnant again, thus causing a decrease in child numbers [19]. In terms of the relationship between sibling numbers and ADHD, we do not think that having a child with ADHD will affect the number of children in the family on condition that the child concerned is not the first to be born.

The number of children in the family has been shown to affect parental child-raising attitudes in the literature, with parents exhibiting less emotional warmth, interest, and overprotection as the number of children rises [24]. Children diagnosed with ADHD have been found to feel that they experience less acceptance and interest from their parents as their oppositional symptoms increase, and that they are subjected to more disciplining from parents [25]. When the children with ADHD were evaluated among themselves in the present study, a positive correlation was determined between the number of siblings and oppositional subscale scores. We think that the number of siblings may affect parental attitudes and lead to the development of oppositional behaviors in individuals diagnosed with ADHD.

This study will make an important contribution to the literature by examining birth order and number of siblings in children with ADHD. However, there are also a number of limitations to this research. The most important of these lies in its cross-sectional nature. Another limitation is that a self-report tool completed only by mothers was employed to determine the severity of ADHD.

In conclusion, no difference was determined in this study between children with ADHD and healthy controls in terms of birth order or number of siblings. Evaluation of the children with ADHD revealed positive correlations between birth order and hyperactivity and opposition subscale scores. A positive correlation was also determined in the children with ADHD between number of siblings and oppositional symptoms. We think that these findings should be borne in mind in future research into the causes of ADHD.

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ORCID and Author contribution: O.K. (0000-0002-7504-5604), T.K. (0000-0002-2156-3457), P.A.A. (0000-0001-5938-3243) and T.K. (0000-0002-0313-558X). All authors contributed to the manuscript conception, design, literatüre research, writing, critical review and final approval.

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RESEARCH ARTICLE

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Comparison of Pre-Hospital Preliminary Diagnosis and Definitive Diagnosis in Emergency Department

Hastane Öncesi Konulan Ön Tanı ile Acil Serviste Konulan Kesin Tanıların Karşılaştırılması

Yusuf Kantar[1], Necmi Baykan[2]*, Funda İpekten[3], Melih İmamoğlu[4]

1.Emergency Service, Akçaabat Haçkalıbaba State Hospital, Trabzon, Türkiye
2.Emergency Department, Kayseri City Hospital, Kayseri, Türkiye
3.Biostatistics Department, Adıyaman University School of Medicine, Adıyaman, Türkiye
4.Emergency Department, Karadeniz Technical University School of Medicine, Trabzon, Türkiye

ABSTRACT

Aim: In this study, it was examined whether the anamnesis taken by pre-hospital paramedics and the physical examination performed in a limited time were effective as intended in non-trauma patients brought to a secondary level district state hospital by ambulance. In addition, it was evaluated whether appropriate preliminary diagnoses were made during the evaluations and these preliminary diagnoses were compared with the definitive diagnoses made after the examinations performed in the emergency room.
Methods: Between 01.01.2023 and 30.06.2023, patients brought to a State Hospital by ambulance were retrospectively analyzed. All age groups brought from the field for non-traumatic reasons were included in the study. Patients referred from another hospital, admitted to another ward for hospitalization and brought to the emergency department with cardiopulmonary arrest were not included in the study.
Results: During the study period, all patients brought to our emergency department by ambulance were examined. The mean age of the patients was 66. More than half of the cases were female (57.7%). When we compared which system in the body the symptoms and preliminary diagnoses considered by the paramedics belonged to and which system the definitive diagnoses made in the emergency department belonged to, it was observed that there was a statistically moderate level of agreement between the pathologies considered by the 112 teams and the pathologies considered by the emergency department physicians in all body systems except genitourinary system **pathologies (Kappa 0.558).**
Conclusion: It was observed that the preliminary diagnosis or symptom stated in the case form by ambulance workers working in prehospital emergency health services was similar to the definitive diagnostic systems in the emergency department. However, it was determined that 74.9% of the case forms stated symptoms instead of preliminary diagnosis. This may be due to paramedics not wanting to take responsibility by stating a more general approach to patient handover.

Keywords: Definitive diagnosis, Emergency department, Preliminary diagnosis

ÖZ

Amaç: Bu çalışmada ambulansla ikinci basamak bir ilçe devlet hastanesine getirilen travma dışı hastalarda hastane öncesi paramediklerin aldığı anemnez ve kısıtlı sürede yaptığı fizik muayenenin hedeflenen etkinliği gösterip göstermediği incelenmiştir. Ayrıca yapılan değerlendirmelerde uygun ön tanıların konulup konulmadığı değerlendirilmiş ve bu ön tanılar acil serviste yapılan muayeneler **sonrası konulan kesin tanılarla karşılaştırılmıştır.**
Yöntemler: 01.01.2023 ile 30.06.2023 tarihleri arasında bir Devlet Hastanesine ambulans ile getirilen hastalar retrospektif olarak incelendi. Travma dışı nedenlerle sahadan getirilen tüm yaş grupları çalışmaya dahil edildi. Başka bir hastaneden sevk edilen ve kardiyopulmoner arrest ile acil servise getirilen hastalar çalışmaya dahil edilmedi.
Bulgular: Çalışma süresi boyunca acil servisimize ambulans ile getirilen tüm hastalar incelendi. Hastaların yaş ortalaması 66 idi. Olguların yarısından fazlası kadındı (%57,7). Paramedikler tarafından düşünülen semptom ve ön tanıların vücuttaki hangi sisteme dahil oldukları ile acil serviste konulan kesin tanıların hangi sisteme dahil oldukları karşılaştırıldığında, 112 ekipleri tarafından düşünülen patolojiler ile acil servis hekimleri tarafından düşünülen patolojiler arasında genitoüriner sistem patolojileri hariç tüm vücut sistemlerinde istatistiksel olarak orta düzeyde bir uyum olduğu görüldü (Kappa 0.558).
Sonuç: Hastane öncesi acil sağlık hizmetlerinde görev yapan ambulans çalışanlarının vaka formunda belirttikleri ön tanı veya semptomun acil servisteki kesin tanı sistemleri ile benzer olduğu görülmüştür. Ancak vaka formlarının %74,9'unda ön tanı yerine semptom belirtildiği tespit edilmiştir. Bu durum, paramediklerin hasta tesliminde daha genel bir yaklaşım belirterek sorumluluk almak istememelerinden kaynaklanmış olabilir.

Anahtar Kelimeler: Acil tıp, Kesin tanı, Ön tanı

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*Corresponding Author: Necmi Baykan, Assoc.Prof. Emergency Department, Kayseri City Hospital, Muhsin Yazıcıoğlu Street No:77 Kocasinan, Kayseri, Türkiye, Phone: +905063963930 / mail: drnecmibaykan@gmail.com

ORCID: 0000-0002-6845-9550

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Introduction

Emergency medicine is a branch of science established to urgently detect life-threatening clinical conditions of patients, to provide the necessary examinations and treatments in a short time and to contribute to the well-being of people [1]. Another task of emergency medicine is to identify pre-hospital vital situations in the field, to start the necessary treatment at the scene or to transfer the case to an appropriate health institution [2]. The main purpose of pre-hospital emergency health services is to provide the necessary intervention in disasters, major traumatic events or emergencies due to chronic diseases and to contribute to the reduction of morbidity and mortality rates by transporting the patient. For this purpose, air, land and sea ambulances are used and ambulances are staffed by physicians, emergency medical technicians or paramedics [3]. Personnel who have medical intervention authority in teams without a doctor and who perform drug applications are called paramedics [4]. Paramedic training was first started in 2000, and as the years progressed, the number of schools, the number of graduates and the number of public employment increased, and then the quality and standardization of education started to be discussed [5]. In this context, the protocol defining the definition of profession, powers and responsibilities was published in 2009, but the lack of updates afterwards has led to various issues [6]. It is expected from the ambulance team working before the hospital to keep records about the patient intervened. These records are very important in order to be accessed by the health personnel who evaluate the patient later or to be applied in case of a legal problem, and this issue is also supported by institutions providing international quality and accreditation services [7].

In this study, it was evaluated whether the anamnesis taken by paramedics before the hospital and the physical examination performed by paramedics in a limited time in non-traumatic patients brought to a second-level district state hospital by ambulance showed targeted effectiveness and whether the appropriate preliminary diagnosis was made in the evaluations made, and these preliminary diagnoses were compared with the definitive diagnoses made after the examinations in the emergency department.

Methods

Between 01.01.2023 and 30.06.2023, patients brought to Akçaabat Haçkalıbaba State Hospital by ambulance were retrospectively analyzed. Male and female patients of all age groups brought from the field for non-traumatic reasons were included in the study. Patients referred from another hospital, admitted to another ward for hospitalization and brought to the emergency department with cardiopulmonary arrest were not included in the study. Approval for our study was obtained from the ethics committee of Karadeniz Technical University Faculty of Medicine (Ethics Committee Decision Date: 08.11.2023 and No: 2023/199). The data were recorded on pre-prepared data forms with the information obtained from the transport forms filled out by 112 ambulance teams and the patient application registration system. Cases with missing data were not included in the study. The age, gender, chronic diseases, the body system to which the symptom or preliminary diagnosis belonged at the first evaluation by 112 teams and thefinal definitive diagnosis of the patient in the emergency department were recorded on the data collection forms. Conditions such as general condition disorder, hyperglycemia, hypoglycemia, high fever, anemia were grouped under the title of other systems. Accordingly, a comparison was made between the preliminary diagnosis considered by prehospital paramedics and the definitive diagnoses made in the emergency department. The study included 808 patients.

The conformity of the data to normal distribution was evaluated by histogram, Q-Q graphs and Shapiro-Wilk test. Kappa statistics were used to evaluate the concordance of pre-hospital preliminary diagnostic systems with hospital definitive diagnostic systems. Sensitivity, selectivity, positive and negative predictive values are given with 95% confidence intervals. Data were analyzed using R 4.3.2 (www.r-project.org) software. Significance level was accepted as $p<0.05$.

Results

During the study period, all patients brought to

our emergency department by ambulance for non-traumatic reasons were examined. The mean age of the patients was 66 years. More than half of the cases were female (57.7%). When the case forms were analyzed, it was found that 9.7% of the 112 teams wrote "general condition disorder" in the section of the form where the symptom or preliminary diagnosis should be specified (Table 1).

Table 1. Demographic characteristics and vital signs of the patients and data of patients evaluated as general status disorder

Female	466 (57.7)
Male	342 (42.3)
Average Age	66.05±21.15
Vital Signs	
Body temperature (°C)	36.35±1.12
Pulse rate (/min)	89.77±20.08
Systolic blood pressure (mmHg)	128.29±30.89
Diastolic blood pressure (mmHg)	76.82±16.54
Content of the information written on the case form	
Symptom	605(74.9)
Preliminary diagnosis	125(15.5)
General Condition Disorder	78(9.7)
Patients assessed as having a general condition disorder (n=78)	
Average Age	80.15±14.24
Definitive diagnostic system	
Respiratory	25(32.1)
Genitourinary	21(26.9)
Neurological	10(12.8)
Cardiovascular	7(9.0)
Musculoskeletal	7(9.0)
Gastrointestinal	2(2.6)
Other	6(7.7)
Ending in the Emergency Department	
Discharged	42(53.8)
Service hospitalization	22(28.2)
Intensive Care Unit hospitalization	9(11.5)
Referred	5(6.4)

Data are expressed as mean±standard deviation and n(%)

Analyzing the patients who were brought to the emergency department by ambulance and whose general condition disorder was written on the case form, it was observed that the mean age was 80 years, respiratory diseases were detected most frequently and more than half of them were discharged from the emergency department (Table 1). Of the 56 patients with a history of Alzheimer's disease, 24 (42.9%) had a prediagnosis of general condition disorder written on the case submission form.

Evaluation of the medical history of the patients included in the study revealed that 52.7% of the patients did not indicate whether they had any disease in their medical history on the 112 case form. Hypertension was the most common disease (22.5%) among the cases with a specified history (Table 2).

Table 2. Diseases in the medical history of the cases and systems in which symptoms or prediagnoses are associated according to vital signs

History of disease	n(%)	
Hypertension	182 (22.5)	
Diabetus Mellitus	103 (12.7)	
Coronary Artery Disease	100 (12.4)	
Alzheimer's	56 (6.9)	
Chronic Obstructive Pulmonary Disease	49 (6.1)	
Cerebrovascular Disease	47 (5.8)	
Malignancy	37 (4.6)	
Chronic Renal Failure	11 (1.4)	
Epilepsy	9 (1.1)	
Benign Prostatic Hyperplasia	2 (0.2)	
Amyotrophic Lateral Sclerosis	2 (0.2)	
Schizophrenia	2 (0.2)	
Parkinson	1 (0.1)	
Unspecified	426 (52.7)	
Systems to which the symptoms or prediagnoses considered by paramedics belong	Cases with systolic blood pressure of 140 mmHg and above (n:313)	Cases with fever of 38 °C and above (n:30)
Cardiovascular	73(23.3)	5(16.7)
Neurological	61(19.5)	2(6.7)
Gastrointestinal	55(17.6)	5(16.7)
Respiratory	47(15.0)	8(26.7)
Musculoskeletal	19(6.1)	-
Genitourinary	8(2.6)	-
Obstetric gynecological	1(0.3)	-
Psychiatric	9(2.9)	1(3.3)
Other	40(12.8)	9(30.0)

Data are expressed as n (%)

On the case submission form, the most frequently marked symptom or prediagnostic system was the cardiovascular system in patients whose systolic blood pressure was measured at 140 mmHg and above (23.3%), while this was found to be "other" systems in patients whose fever was measured at

38 °C and above (30%) (Table 2).

Comparison of the body systems belonging to the symptoms and preliminary diagnoses considered by the paramedics with the body systems belonging to the definitive diagnoses made in the emergency department showed a statistically moderate level of agreement between the pathologies considered by the 112 teams and the pathologies considered by the emergency department physicians in all body systems except the pathologies of the genitourinary system (Kappa 0.558). The diseases with the highest rates of compliance were obstetric and gynecological and psychiatric diseases (Table 3).

Discussion

The emergency medicine system is a system that covers the entire period between the notification of a disease or suspected disease and the treatment of that condition. The hospital part of this system is composed of emergency services and the pre-hospital part of this system is composed of teams working in ambulances [8]. The personnel working in the pre-hospital health system in our country are mostly emergency medical technicians and paramedics [9]. Ambulance crew members are expected to record patient information on standardized forms for each patient they transport. This information can be used later by health professionals and lawyers as both medical and legal records [7].

In our study, it was observed that there was a moderate level of agreement between the symptoms and preliminary diagnoses considered by ambulance workers responsible for prehospital health services and the definitive diagnoses made by emergency department physicians in patients transported from the field to the emergency department.

In the study by Sarı et al. 54.1% of the patients arriving by ambulance were male and 45.9% were female. In the study conducted by Bozatlı et al. in our country, 52.9% of the patients were male and 47.1% were female. In the study conducted by Yıldız et al. the male rate was 60.5% and the female rate was 39.5% [10,11]. In our study, the female to male ratio was 57.7% female and 42.3% male, which is different from the studies conducted in our country, but similar to the studies conducted in other countries [12,13]. The reason for the data in our study may be thought to be due to the fact that the center where the study was conducted serves a certain region and the demographic distribution of the people living in this region.

While the mean age in our study was similar to the study by Bozatlı et al. [1], In other studies conducted in our country, the average age was found to be 47 years [11,14]. The high mean age may be attributed to the fact that pediatric patients were not transported to this hospital by 112 since there was no pediatric emergency department as a separate unit in the hospital where the study was conducted and trauma patients were not included in the study.

In a study conducted by Sarı et al. in a tertiary emergency department, the most frequently mentioned systems among the preliminary diagnoses considered by paramedics in patients admitted with 112 were gastrointestinal system, cardiovascular system and neurological system. In our study, these systems were ranked in the top three and are similar in this respect. In the same study, respiratory causes were not in the top three among the definitive diagnoses made in the emergency department [10], in our study, respiratory system was the most frequently diagnosed system. In the study conducted by Yılmaz et al. in our country, cardiovascular, respiratory and neurologic systems were in the first three ranks among the preliminary diagnoses of the ambulance team, respectively [15]. This study is not similar to our study. Similar to our study, in the study of Önge et al. the most frequently mentioned systems by the ambulance crew were neurological, cardiac and gastrointestinal systems [16]. It is thought that the patients in the region where our study was conducted have a different sociocultural structure compared to the patient groups in other studies.

Although discharge rates from the emergency department are lower than our study in some studies [17,18], it is similar to the study of Önge et al [16]. The high rate of discharge of patients arriving by ambulance from the emergency department is one of the indicators of inappropriate use of ambulances according to a meta-analysis

Table 3. Concordance rates of prehospital and hospital diagnoses

Systems to which the symptom or precipitant considered by 112 belongs n(%)	Systems to which the definitive diagnoses made in the emergency department belong n(%)										
	Cardio vascular eurological	Neurological	Gastro intestinal	Respiratory	Musculo skeletal	Genito urinary	Obstetric gynecological	Psychiatric	Other	Kappa	p
Cardiovascular	82(66.7)	13(9.0)	8(6.7)	17(9.1)	3(6.0)	12(11.0)	0(0.0)	2(5.7)	5(14.3)	0.588	<0.001
Neurological	7(5.7)	110(76.4)	6(5.0)	6(3.2)	7(14.0)	2(2.8)	0(0.0)	3(8.6)	2(5.7)		
Gastrointestinal	7(5.7)	3(2.1)	94(79.0)	9(4.8)	1(2.0)	32(29.4)	1(16.7)	1(2.9)	0(0.0)		
Respiratory	8(6.5)	3(2.1)	2(1.7)	116(62.0)	1(2.0)	5(4.6)	0(0.0)	0(0.0)	1(2.9)		
Musculoskeletal	7(5.0)	0(0.0)	4(3.4)	6(3.2)	31(62.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)		
Genitourinary	0(0.0)	0(0.0)	0(0.0)	1(0.5)	0(0.0)	29(26.6)	0(0.0)	0(0.0)	1(2.9)		
Obstetric gynecological	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	5(83.3)	0(0.0)	0(0.0)		
Psychiatric	3(2.4)	2(1.4)	1(0.8)	1(0.5)	0(0.0)	0(0.0)	0(0.0)	29(82.9)	0(0.0)		
Other	9(7.3)	13(9.0)	4(3.4)	31(16.6)	7(14.0)	28(25.7)	0(0.0)	0(0.0)	26(74.3)		
Total	123 (100)	144 (100)	119 (100)	187 (100)	50 (100)	109 (100)	6 (100)	35 (100)	35 (100)		

by Snooks et al [19]. Evaluation of hospitalization and referral rates, the study of Atilla et al. shows similar rates with our study [17]. The reason why the exitus rates in our study were considerably lower compared to other studies in the literature may be due to the fact that patients brought to the emergency department with cardiopulmonary arrest were not included in the study and that critically ill patients were referred because the hospital where the study was conducted was a district state hospital.

In our study, some patients transported by paramedics did not have any symptoms or prediagnosis of any body system and were delivered to the emergency department on the grounds of general condition disorder. When these cases were analyzed, it was observed that the average age was 80 years and 42.9% of the patients with a history of Alzheimer's disease presented with this complaint. Based on these data, it can be concluded that 112 teams have difficulty in taking anamnesis from geriatric patients, they cannot fully understand the complaints of patients with difficulties in expressing themselves such as Alzheimer's disease, and as a result, they use an expression such as general condition disorder instead of trying to determine the real complaint or preliminary diagnosis of the patients.

On the case submission form, the most frequently marked symptom or prediagnostic system was the cardiovascular system in patients whose systolic blood pressure was measured at 140 mmHg and above (23.3%), while this was found to be "other" systems in patients whose fever was measured at 38 °C and above (30%). This may be due to paramedics writing "hypertension" or "high fever" in the preliminary diagnosis section of the case form, regardless of the patient's complaint or examination. In other words, while the ambulance team can make a preliminary diagnosis of an existing infection by asking a few more questions to a patient with high fever while evaluating the case, patients delivered to the emergency department with only "high fever" may cause both deficiencies in pre-hospital care and delays in hospital functioning. Similarly, the same problems can be seen when a patient with high blood pressure is admitted to the emergency room with a "complaint of hypertension" instead of trying to determine which system this abnormality belongs to.

When the preliminary diagnoses considered by the paramedics before the hospital were compared with the definitive diagnoses made in the hospital, it was observed that the highest rate of similarity was observed in obstetric and gynecological diseases and psychiatric diseases. This may be due to the small number of patients in the obstetric

diseases category and the fact that these patients are pregnant patients. On the other hand, although the correct decision was made in the majority of patients in the psychiatric complaints category, it was observed that 13.8% of the patients who were evaluated as psychiatric cases by the ambulance teams had a definitive diagnosis of cardiovascular and neurological systems.

Conclusion

As a result, it was observed that the preliminary diagnosis or symptom stated in the case form by ambulance workers working in prehospital emergency health services was similar to the definitive diagnostic systems in the emergency department. However, it was found that 74.9% of the case forms indicated symptoms instead of preliminary diagnosis. This may have been due to the fact that the paramedics did not want to take responsibility by taking a more general approach in handing over the patient.

With special trainings to be given to paramedics and emergency medical technicians, their ability to take anamnesis in a limited time and to perform effective and targeted physical examinations can be improved, and in this way, both pre-hospital triage and referral of patients to appropriate centers and pre-hospital medical treatment can be provided without delay.

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Effect of Tocilizumab Treatment on Seroconversion in Hyperinflammation Secondary to Covid 19

Covid 19'a Bağlı Hiperinflamasyonda Tocilizumab Tedavisinin Serokonversiyon Üzerine Etkisi

Faruk Karandere[1], Deniz Yılmaz[1], Felemez Arslan[1*], Ezgi Şahin[1], Hakan Koçoglu[1], Nilgun Işıksaçan[2],

1.University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Internal Medicine, Istanbul, Turkiye.
2.University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Biochemistry, Istanbul, Turkiye

ABSTRACT

Aim: During the ongoing COVID-19 pandemic, the management of hyperinflammation, a serious symptom that occurs secondary to the disease, has emerged as a major challenge. Tocilizumab, an immunosuppressive drug, offers a potential solution. However, it is extremely important to understand its effects on antibody formation after recovery from Covid-19. Therefore, our study aimed to investigate the effects of tocilizumab treatment on antibody production by measuring SARS-COV-2 spike total antibody levels at the third month post-infection in patients receiving this specific treatment.
Materyal and Methods: Our study incorporated 48 patients diagnosed with Covid 19 who presented with hyperinflammation during hospitalization. These patients, admitted to our institution, were treated with tocilizumab and subsequently discharged. We meticulously determined the 3rd month SARS-COV-2 spike total antibody levels in these patients.
Results: The participants of the study, characterized by a mean age of 52.5 ± 11.6 years, demonstrated positive SARS-COV-2 spike total antibody levels at 3 months, irrespective of age, gender, comorbidity, and length of hospital stay. The mean antibody levels in the patient population were quantified to be 223.58 ± 68.36 U/mL, with a range from 14.2 to 250 U/mL.
Conclusion: Our findings reveal that all patients exhibited positive antibody levels at 3 months following tocilizumab treatment.This suggests that the administration of tocilizumab in the management of hyperinflammation secondary to Covid 19 does not adversely affect antibody formation, at least in the short term. This could have substantial implications for future treatment strategies.

Keywords: Covid 19; IL-6; Hyperinflammation; Tocilizumab; Antibody

ÖZ

Amaç: Devam eden COVID-19 pandemisi sürecinde, hastalığa ikincil olarak ortaya çıkan ciddi bir semptom olan hiperinflamasyonun yönetimi büyük bir meydan okuma olarak karşımıza çıkmıştır. İmmünsüpresif bir ilaç olan Tocilizumab, potansiyel bir çözüm sunmaktadır. Ancak, Covid-19'dan iyileşme sonrası antikor oluşumu üzerindeki etkilerini anlamak son derece önemlidir. Bu nedenle, çalışmamız bu spesifik tedaviyi alan hastalarda, enfeksiyon sonrası üçüncü ayda SARS-COV-2 spike toplam antikor seviyelerini ölçerek, tocilizumab tedavisinin antikor üretimi üzerindeki etkilerini araştırmayı amaçlamıştır.
Yöntemler: Çalışmamız, hastaneye yatırıldıkları sırada hiperinflamasyon gösteren ve Covid-19 tanısı almış 48 hastayı içermektedir. Bu hastalar kurumumuza kabul edilmiş, tocilizumab ile tedavi edilmiş ve sonrasında taburcu edilmişlerdir. Bu hastaların 3. ay SARS-COV-2 spike toplam antikor seviyeleri titizlikle belirlenmiştir.
Bulgular: Çalışmanın katılımcıları, ortalama yaşları 52,5 ± 11,6 olan, yaş, cinsiyet, komorbidite ve hastanede kalış süresi ne olursa olsun 3. ayda pozitif SARS-COV-2 spike toplam antikor seviyeleri göstermiştir. Hastaların ortalama antikor seviyeleri 223,58 ± 68,36 U/mL olarak ölçülmüş, aralık 14,2 ile 250 U/mL arasında değişmiştir.
Sonuç: Bulgularımız, tüm hastaların tocilizumab tedavisi sonrası 3 ayda pozitif antikor seviyeleri sergilediklerini ortaya koymaktadır. Bu, hiperinflamasyonun Covid 19'a ikincil yönetiminde tocilizumab uygulamasının, en azından kısa vadede, antikor oluşumunu olumsuz etkilemediğini göstermektedir. Bu, gelecekteki tedavi stratejileri için önemli sonuçlar doğurabilir.

Anahtar Kelimeler: Covid 19; IL-6; Hiperinflamasyon; Tocilizumab; Antikor

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*Corresponding Author: Felemez Arslan, MD, University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Zuhuratbaba Mah, Dr. Tevfik Sağlam Cd No:11, 34147, Bakırköy, İstanbul, Turkiye. Phone: +905438355797 / mail: feloarslan@gmail.com

Orcid: 0000-0001-8318-1860

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Introduction

Severe disease due to Covid-19 can occur in healthy individuals of any age, but mostly male gender, advanced age or it is even more fatal in patients with underlying comorbidities such as cardiovascular disease (CVD), Diabetes Mellitus (DM), chronic kidney disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), and cancer [1-3]. It has been observed that a hyper-inflammatory picture associated with high inflammatory markers and serum cytokine levels causes severe morbidity and mortality in a significant proportion of COVID-19 patients, with or without concomitant comorbidity [4].

Besides, it is not clear at what stage of the disease, in which patients this hyperinflammation associated with Covid-19 occurs, and when the breaking point is, it has not been revealed in the treatment algorithm yet [5]. However, cytokine inhibition and other immunomodulation treatments are applied by many centres in order to break the hyperinflammation picture [6].

While circulating IL-6 levels are extremely low in healthy individuals, a significant increase in plasma IL-6 level has been observed, especially in patients with covid-induced hyperinflammation, and it has been shown that this is strongly associated with severe disease [7-8]. In some studies, it has been observed that blocking IL-6 reduces the hyperinflammation caused by Covid-19, and Tocilizumab, an anti-IL-6 receptor antibody given for this purpose, prevents hyperinflammation in patients and positive results are obtained [9-10].

Studies hitherto for seroconversion against Covid-19 infection show that the seropositivity of antibody testing in the first week after onset of illness is unsatisfactory in many cases. However, while IgM increased at the beginning of the disease, it decreased over time, and IgG antibody reached its highest levels from the second week in many studies [11]. Xiao et al. In his study, it was shown that IgG remained positive from the 5th week, but IgM continued to decrease [12]. However, studies showing antibody response in patients using immunosuppressive agents were not observed.

Although different immunomodulators or immunosuppressive agents are used in many centres during the treatment phase of Covid-19, no study has been review in literature with the antibody responses of these patients. In our study, we detected the antibody level in the 3rd month after the disease in patients who were hospitalized in a pandemic hospital and were given 4-8mg/kg Tocilizumab at a dose of 4-8mg/kg due to hyperinflammation, and that these drugs used in patients using Tocilizumab treatment, etc. We aimed to determine whether it has an effect on antibody formation.

Material and Methods

This study is a prospective, cohort study and of 48 RT –PCR positive COVID -19 patients who were hospitalized at University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital in Istanbul, Turkey. Patients were tested for SARS –CoV–2 based on epidemiological and clinical criteria as outlined in the National Guideline for the Diagnosis and Treatment Protocol for SARS–CoV–2 Infection that was published and updated by Turkish Ministry of Health. Nasopharyngeal and oropharyngeal specimens were collected once from patients and specimens were tested for SARS–CoV–2 using real-time RT –PCR at our hospital. Informed consent was obtained from each subject prior to the study.

The Medical Research Ethics Committee of the University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital approved the study. We are committed to protecting patient privacy and complying with the Helsinki Declaration. (Ethical approval date: 02.11.2020, Approval number: 2020-22-05).

The total number of patients hospitalized in the COVID service in our hospital between October 2020 and June 2021, Tocilizumab treatment was given to 104 patients. 44 patients who bears the following exclusion criteria was excluded from work. The remaining 60 patients were called for antibody tests at the 3rd month, but 12 patients could not be contacted for various reasons. Thus, Forty-eight patients whose 3rd month antibody results were suitable for the inclusion and exclusion criteria were included into our study. Last patient was accepted in March 2021 and the study was terminated in June 2021 (See figure 1

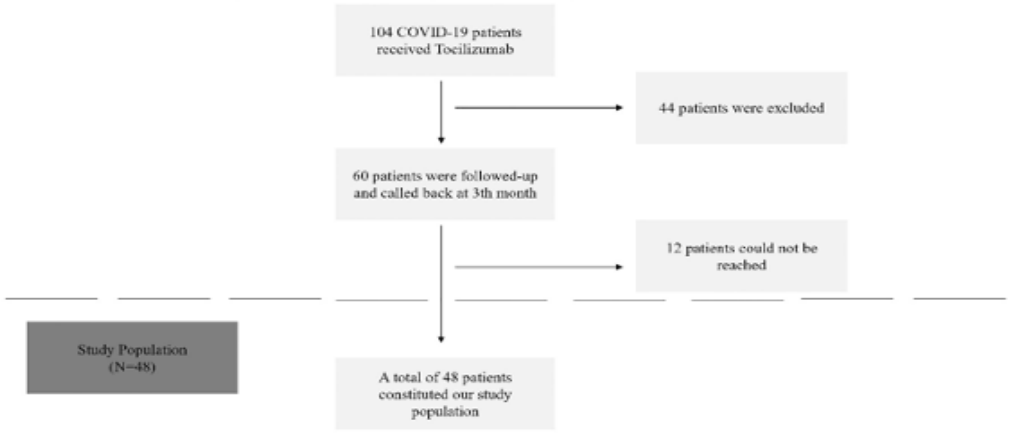

Figure 1: Flow Diagram for Study Participants From October 2020 to June 2021, 104 patients received Tocilizumab at our hospital. After excluding 44 based on specific criteria, we sought to test the remaining 60 for antibodies at 3 months. Unable to reach 12, we included 48 patients with valid antibody results in our study, which concluded in June 2021.

for study flow).

Criteria for inclusion in the study:

1- >= being over 18 years old

2- Tocilizumab treatment given during the patient's hospitalization

Exclusion criteria from the study:

1- Death status during or after treatment

2- Patients <18 years old

3- Pregnant patients

4- Refusing to participate in the study

5- The patient has no previous history of COVID

6- Receiving a different immunosuppressive treatment due to comorbidities or after discharge patients on an immunosuppressive therapy

7- Those given additional immunosuppressive therapy during COVID-19 treatment (e.g.: steroid therapy)

8- Positive real-time PCR test

9- Re-COVID-19 until the time of the 3rd month antibody test after discharge from the hospital have had an infection

10- To have had any covid 19 vaccine

A total of 48 patients constituted our study population. Demographic and clinical information was saved. The patients were invited to the hospital by phone call at the 3rd month and the antibody Blood samples were taken for levels.

Sample Collection and Testing Methods

The Elecsys Anti-SARS-CoV-2 S test is an ECLIA (electrochemiluminescence immunoassay) test used for the in vitro quantitative determination of high-affinity antibodies (including Ig G) against the SARS-CoV-2 Spike(S) protein receptor binding domain. Anti-SARS-CoV-2 measurement was performed following the manufacturer's instructions. Results are reported as numerical values in U/mL as well as non-reactive (<0.8 U/mL; negative) and reactive (≥0.8 U/mL; positive, max: 250 U/mL) results. According to the product information shared by the manufacturer, the sensitivity of the Elecsys® anti-SARS-CoV-2 test for ≥ 14 days is 100% (95% CI: 88.1% - 100%) and the overall specificity is 99.81% (95% CI). : 99, 65-99.91%).

Statistical Analysis

NCSS 2007 (Number Cruncher Statistical System, Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used in evaluation of the study data. Frequency and percentage values of categorical variables, arithmetic mean and standard deviation values of quantitative

variables are presented.

Results

A total of 48 RT-PCR confirmed patients with COVID-19 pneumonia and who were received Tocilizumab theraphy during hospitalization period were included in the study. The mean age of the patients was 52.5 ± 11.6 years. While 87.5% (n=42) of total patients were male, 12.5% were female (n=6). Mean sPO2 at the time of admission was 91.5 ± 4.2% and mean length of hospitalisation was 25.55 ± 15.96 days (Table 1).

Table 1: Demographic characteristics of patients given tocilizumab, length of hospital stay, sPO2 at the time of admission

Gender, n (%)	
Male	42 (87.5%)
Female	6 (12.5%)
Age (years), Mean ± SD	52.5 ± 11.6
sPO2 at the time of admission (%),Mean ± SD	91.5 ± 4.2
Lenght of hospitalisation (days), Mean ± SD	25.55 ± 15.96

Of all patients, 29.2% (n=14) had hypertension; 22.9% (n=11) had diabetes mellitus; 16.7% (n=8) had COPD / Asthma; 10.4% (n=5) had CVD; 4.2% (n=2) had cancer and 10.4% (n=5) had other diseases (Table 2). Of all patients, 2.1% (n=1) had normal, 6.3% (n=3) had mild, 33.3% (n=16) had moderate, and 58.3% (n=28) had severe CT involvement at the time of admission (Table 3).

SARS-COV-2 spike total antibody levels were found to be positive at 3 months in all patients, regardless of age, gender, comorbidity and length of stay. The mean antibody levels of the patients were 223.58 ± 68.36 U/mL (min: 14.2 and max: 250 U/mL) (Table 3).

Table 2: Comorbid disease distribution of patients treated with tocilizumab

Values	Absent n (%)	Present n (%)
Hypertension	34 (70.8%)	14 (29.2%)
Diabetes Mellitus	37 (77.1%)	11 (22.9%)
Chronic obstructive pulmonary disease / Asthma	40 (83.3%)	8 (16.7%)
Cardiovascular disease	43 (89.6%)	5 (10.4%)
Cancer	46 (95.8%)	2 (4.2%)
Other diseases	43 (89.6%)	5 (10.4)

Table 3: CT involvement at the time of admission

Values	Atypical n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
CT involvement at the time of admission	1 (2.1%)	3 (6.3%)	16 (33.3%)	28 (58.3%)
3rd month SARS-COV-2 spike total antibody levels				
Patients with positive total antibody, n (%)				48 (100%)
Total antibody level (U/mL), Mean ± SD				223.58 ± 68.36

Discussion

In our study, the mean age of the patients was found to be 52.5. Of the total patients, 87.5% (n=42) were male and 12.5% were female (n=6). This situation, which was found similar to previous studies, may be associated with a higher incidence of severe Covid 19 infection in men than in women, due to reasons such as stronger immunological response in women than in men [9,13]. As in most studies, the most common comorbidity in our study was hypertension with a rate of 29.2% [14].

Many studies have shown that high levels of inflammatory markers such as crp, ldh, serum ferritin level, serum IL-6 level, etc., are associated with mortality and disease severity in Covid 19 patients [4,7]. The most striking of these inflammatory biomarkers was thought to be the rising IL-6 level [4,18].

Interleukin 6 (IL-6) produced in response to infections and tissue injuries has different biological activities. In addition to the regulation of the acute phase response, it also has the feature of inducing the differentiation of B cells into cells that secrete immunoglobulin [15-17]. For all these effects of IL-6 to occur, it must bind to the IL-6 receptor [17,18]. The detection of high serum IL-6 levels, especially in the hyperinflammation picture associated with Covid 19, drew attention to Tocilizumab, a monoclonal antibody that blocks the already existing IL-6 receptor [17]. Although its effectiveness is debated, tocilizumab has been used by many centres in the treatment of hyperinflammation associated with Covid 19, considering that it may be beneficial and life-saving in patients with COVID-19 [19-21].

In our centre, patients were managed in accordance

with the COVID 19 Guidelines determined by the Ministry of Health of the Republic of Turkey, and Tocilizumab treatment was administered to patients with hyperinflammation [22]. Understanding the duration of long-term immunological memory in Covid 19 patients after the disease is of great importance in terms of both directing vaccination studies and determining the situation of re-exposure to the disease [23]. In studies, virus-specific antibodies were detected approximately 2 weeks after the onset of COVID-19 symptoms in most patients infected with SARS-CoV-2, and although antibody levels decreased over time, it was observed that many patients remained positive in the 3rd month after infection [24, 25].

Unlike these studies, in our study, patients with hyperinflammation due to Covid 19 and who were administered Tocilizumab were selected as the patient group. SARS-COV-2 spike total antibody levels of these patients were found to be positive at 3 months, similar to other studies, regardless of age, gender, comorbidity, and length of stay. There was no negative effect of the administered dose of Tocilizumab on antibody formation, and the results were similar to those of other patients.

The development of long-term immunological memory is based on humoral and cellular immune responses. Studies have shown that vaccines administered against various viral infections in patients with diseases such as Multiple Sclerosis (MS) using immunosuppressive agents have shown that immunosuppressives reduce the humoral and cellular response [23].

In addition, in another study conducted in patients with rheumatoid arthritis, it was shown that short-term use of Tocilizumab did not reduce the humoral response of patients to Pneumococcal Polysaccharide Vaccine (PPV23) and Tetanus Toxoid Vaccine (TTV) vaccines.

In conclusion, IL-6 is an important factor in the transformation of B cells into antibody-secreting cells. Therefore, knowing the effects of IL-6 blocking on antibody formation may be important both in vaccination studies and in predicting the duration of the response to viral infections in patients using IL-6 blocking drugs for various reasons. Therefore, comprehensive multicentre studies are needed.

Conclusion

As a result of our study, we observed that antibody levels were positive in all patients at the 3rd month after Tocilizumab treatment and that Tocilizumab treatment did not have a negative effect on antibody formation, at least in the short term.

Limitations

This study has several limitations. First, we were only able to include a limited number of patients and viral load data were not available. In addition, the limited number of patients did not allow us to adjust for potential confounding factors that could influence antibody response, such as comorbidities, gender, and age. Another important limitation of our study is that it was planned to monitor antibody levels by taking blood samples from patients 3, 6, 9 and 12 months after the onset of COVID 19 symptoms. However, since the vaccination policy has changed in our country, we could only measure antibody levels in the third month after infection.

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Detailed Coccygeal Morphology on Multislice 3d Ct in 1000 Asymptomatic Turkish Adults

1000 Asemptomatik Türk Erişkinin Multislice 3d Ct'de Ayrıntılı Koksigeal Morfolojisi

Turgut Kuytu[1*], Ahmet Karaoğlu[2]

1.VM Medical Park Bursa Hospital, Istinye University, Department of Neurosurgery, Bursa, Türkiye
2.Yüksek Ihtisas Education and Research Hospital, Department of Neurosurgery, Bursa, Türkiye

ABSTRACT

Aim: The morphology of the coccyx varies. This variety makes it difficult to understand the radiologic pathologies in idiopathic coccydynia. This study aimed to examine the coccyx morphology in Turkish society in order to establish a set of societal reference values.
Method: By retrospective analysis of computed tomography scans of one thousand adults, the following were evaluated: number of coccygeal segments, type of coccyxes, sacrococcygeal and intercoccygeal joint fusion, coccygeal spicules, sacrococcygeal straight length, sacrococcygeal and intercoccygeal curvature angles and lateral deviation of the coccyx tip.
Results:The most common number of coccygeal segments was determined to be four, and the most common coccyx type was II. Sacrococcygeal fusion was observed in 69.5%, and intercoccygeal fusion in 83.6%. Coccygeal spicule was seen in 3.7% of the cases. The mean sacrococcygeal straight length was 34.3 mm in males and 32.2 mm in females; this length was also significantly higher in the male group ($p<0.001$). The mean sacrococcygeal curvature angle was 108.8° in females and 112.7° males; this angle was significantly wider in the male group ($p<0.001$).
Conclusion: This study, conducted in asymptomatic Turkish individuals, is the most comprehensive study to date and can be used as a "set of societal reference values" in future studies with symptomatic cases to determine the societal morphology of the coccyx and the etiology of coccydynia.
Key words: Coccyx, Morphology, Turkish, Computed tomography

ÖZ

Amaç: Kuyruk sokumu morfolojisi değişiklik göstermektedir. Bu çeşitlilik idiyopatik koksidinideki radyolojik patolojilerin anlaşılmasını zorlaştırmaktadır. Bu çalışma, bir dizi toplumsal referans değeri oluşturmak için Türk toplumundaki kuyruk sokumu morfolojisini incelemeyi amaçlamıştır.
Yöntem: Bin yetişkinin bilgisayarli tomografi taramasının retrospektif analizi ile aşağıdakiler değerlendirilmiştir: koksigeal segment sayısı, koksiks tipi, sakrokoksigeal ve interkoksigeal eklem füzyonu, koksigeal spiküller, sakrokoksigeal düz uzunluk, sakrokoksigeal ve interkoksigeal eğrilik açıları ve kuyruk sokumu ucunun lateral sapması.
Bulgular: En sık görülen koksiks segment sayısı dört, en sık görülen koksiks tipi ise II olarak belirlenmiştir. Sakrokoksigeal füzyon %69,5, interkoksigeal füzyon ise %83,6 sıklıktadır. Olguların %3,7'sinde koksigeal spikül görülmüştür. Ortalama sakrokoksigeal düz uzunluk erkeklerde 34,3 mm, kadınlarda 32,2 mm idi; bu uzunluk da erkek grupta anlamlı olarak daha yüksekti ($p<0,001$). Ortalama sakrokoksigeal eğrilik açısı kadınlarda 108,8°, erkeklerde 112,7°; bu açı erkek grupta anlamlı olarak daha genişti ($p<0,001$).
Sonuç: Asemptomatik Türk bireylerde yapılan bu çalışma bugüne kadar yapılan en kapsamlı çalışma olup, gelecekte semptomatik olgularla yapılacak çalışmalarda kuyruk sokumu kemiğinin toplumsal morfolojisi ve koksidini etiyolojisinin belirlenmesi amacıyla "toplumsal referans değerleri seti" olarak kullanılabilir.
Anahtar kelimeler: Kuyruk Sokumu, Morfoloji, Türk, Bilgisayarlı Tomografi

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*Corresponding Author: Turgut Kuytu, MD., VM Medical Park Bursa Hospital, Istinye University, Department of Neurosurgery, Bursa, Türkiye. mail: tkuytuu@yaani.com Phone:05324453903

ORCID: 0000-0002-0505-3027

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Introduction

The term coccydynia means pain in or around the coccyx. It most commonly develops secondary to axial trauma to the tailbone [1,2]. Although different studies have defined some etiological factors, such as abnormal coccygeal mobility secondary to a difficult birth, postural changes, tumors, and infections, in around one-third of the cases, the cause is idiopathic [2–4].

Pain is typical of leaning backward and sitting on hard surfaces [5]. It is observed to be more common in obese cases and female patients [6]. Since the morphology of the coccyx varies among people and societies, determining the detailed coccyx morphology for different ethnic groups may provide an advantage in understanding the etiopathogenesis of idiopathic coccydynia.

The coccyx is the last and lowest part of the vertebral column [5]. It comprises an apex, base, anterior surface, posterior surface, and two lateral surfaces [7]. The base is at the highest level, while the apex is at the inferior terminal portion of the vertebral column [8].

The coccyx is not a single bone structure; it consists of 2–5 bony structures. Within the framework of bone structures, fibrous tendons and ligaments restrict movement [9]. The coccyx is connected to the sacrum via the sacrococcygeal joint. Depending on the body position, the pelvis's coccyx and other bony structures move inward or outward to stabilize the spine [10]. Additionally, the coccyx provides support from below to the organs within the pelvis, offers positional support to the anus, and serves as a point of attachment for the pelvic floor tendons [5]. Studies on the structure of the coccyx in different populations use cadavers or plain radiographs and CT and MRI [11–17]. In these studies, in addition to the differences among people, variations were observed in the coccyx structure between societies [11].

In this study, the coccyx morphology of the Turkish population has been comprehensively investigated. The morphological analysis was conducted on cases with different complaints rather than coccydynia patients. Consequently, detailed information regarding the morphological characteristics of the coccyx will be standardized for the Turkish population. Standardization will play a beneficial role in understanding the etiopathogenesis of idiopathic coccydynia. This study aims to investigate the morphology of the coccyx in the Turkish population and compare our findings with other ethnically based studies in the literature. The goal is to identify inter-population differences and establish a "reference value set" specific to the Turkish population.

Materials and Methods

Study Design and Participants

This study is a retrospective investigation conducted between September 2021 and September 2022, based on the records of a tertiary healthcare center. The study utilized records from 1000 individuals, 534 females and 466 males. The study included individuals who presented to the hospital with complaints unrelated to coccygeal pain. The participants encompassed a broad range of preliminary diagnoses that suggested the necessity for abdominal tomography. The participants were registered in 64 different provinces within the borders of Turkey.

Measurements

Three-dimensional reconstructions of the participants' abdominal tomographies were performed for analysis. Experienced independent radiologists evaluated the CT scans. The non-contrast abdominal spiral CT scans (Siemens Somatom scope 16 slices) were reformatted for multiplanar reconstruction with a thickness of 1 mm, and 3D sacrococcygeal images were obtained. On sagittal CT imaging, the number of coccygeal segments, coccyx type according to the Postacchini and Massobrio classification (Figure-1), presence of fusion at the sacrococcygeal and intercoccygeal junction, presence of coccygeal spicule, sacrococcygeal straight length, sacrococcygeal-intercoccygeal curvature angles and lateral deviation of the coccyx were examined (Figure-2,3). The findings were documented and statistically analyzed separately in two different groups according to sex.

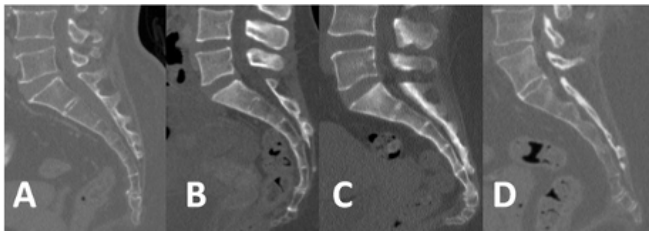

Figure-1: Sagittal reformats showing (A) type I (slightly curved coccyx pointing downwards), (B) type II (more curved coccyx pointing forward), (C) type III (sharply angulated at intercoccygeal joint) and (D) type IV (retroversion of the coccyx) coccyxes

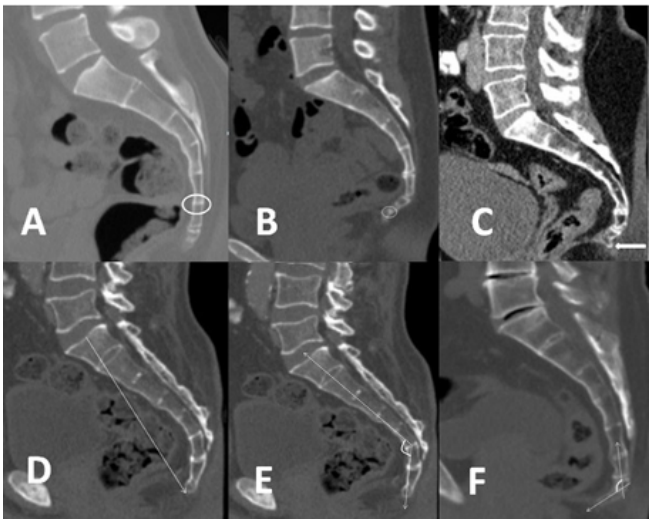

Figure-2; CT images for morphology and morphometry of the sacrococcygeal region. A; Sacrococcygeal fusion. B; Intercoccygeal fusion. C; Coccygeal spicule. D; Sacrococcygeal straight length. E; Sacrococcygeal curvature angle. F; Intercoccygeal curvature angle.

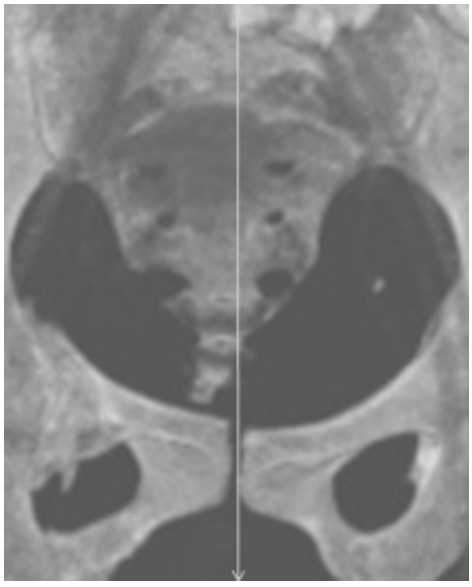

Figure-3; CT image of coccygeal lateral deviation (White arrow represents the midline)

Coccygeal Types

- Type I: Slightly curved coccyx pointing downwards,
- Type II: More curved coccyx pointing forwards,
- Type III: Sharply angulated intercoccygeal joint,
- Type IV: Retroversion of coccyx,
- Sacrococcygeal Fusion: Bony continuity between adjacent vertebrae on all sagittal slices at sacrococcygeal joints
- Intercoccygeal Fusion: Bony continuity between adjacent vertebrae on all sagittal slices at intercoccygeal joints.
- Coccygeal Spicule: Bone projection arising from the terminal coccygeal segment.
- Sacrococcygeal Straight Length: Measured in a straight line from the middle of the upper border of $1 to the tip of the coccyx.
- Sacrococcygeal Curvature Angle: The angle formed by the intersection of a line between the midpoint of the upper borders of the first sacral and first coccygeal vertebra and a line between the upper border of the first coccygeal vertebra and the tip of the coccyx.
- Intercoccygeal Curvature Angle: The angle formed between lines passing across the middle of the first and last coccygeal segments in the median plane.
- Lateral Deviation of the Tip of the Coccyx: This is determined by measuring the angle between the tip of the coccyx and a line passing through the middle of the sacrum.

Exclusion Criteria

- Coccydynia patients.
- Individuals of different ethnicities.
- Those with missing records

2.1 Examined Variables

- Coccyx type according to the Postacchini and Massobrio classification,

- The number of coccygeal segments,
- Presence of fusion at the sacrococcygeal and intercoccygeal junction,
- Presence of coccygeal spicule,
- Sacrococcygeal straight length,
- Sacrococcygeal-intercoccygeal curvature angles and
- Lateral deviation of the coccyx.

Ethics

The principles of the Helsinki Declaration conducted our research. The research has obtained ethical approval from the Istinye University clinical research ethics committee with protocol number 2/2021.K-53. Participation in the study was carried out voluntarily.

Statistical Analysis

The SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The data conformity to normal distribution was evaluated using the Shapiro–Wilkfrancia test. The Mann–Whitney U test was used together with Monte Carlo results to compare two independent groups according to quantitative variables. For the comparison of categorical variables, Pearson Chi-Square and Fisher–Freeman–Halton tests were used with the Monte Carlo Simulation technique, and the comparison of column ratios was expressed using Benjamini–Hochberg corrected p-value results. In order to show how many times those with a risk factor were more than those without, the odds ratio was used with a 95% confidence interval. The quantitative variables were expressed as mean (standard deviation) and median (1st Quartile–3rd Quartile) in the tables, while categorical variables were shown as n (%). The variables were analyzed at a 95% confidence level, and a p-value less than 0.05 was considered significant.

Results

The study included 1000 patients, 534 females and 466 males. The mean age was 55.4±16.8 years (18-99). The number of coccygeal vertebrae ranged between 2 and 5. The number of coccygeal vertebrae observed in the whole group in the order of frequency was 4 (631 cases, 63.1%), 3 (211 cases, 21.1%), 5 (147 cases, 14.7%), and 2 (11 cases, 1.1%). The ranking was the same in the male and female groups (Table 1). The most common coccyx type was type II (725 cases, 72.5%) by a large margin. The second most common coccyx type was type III (193 cases, 19.3%). The rankings for males and females were also the same here (Table 1).

Sacrococcygeal fusion was found in 695 cases (69.5%). The incidence of sacrococcygeal fusion is higher in women (384 cases, 71.9%) than in men (311 cases, 66.7%). However, this finding was not statistically significant (p=0.085). The sacrococcygeal fusion has been identified in 352 cases as complete fusion and in 343 cases as partial fusion. Type II is the most commonly encountered coccyx type characterized by sacrococcygeal fusion, with a prevalence rate of 50.2%. Conversely, type I coccyx is the least commonly observed variant, with a rarity of 0.6% (Table 2).

The number of cases with fusion between one or more coccygeal vertebrae was 836 (83.6%). In 84% (706 cases) of the cases with intercoccygeal fusion, fusion was observed at the most distal intercoccygeal junction. In 26 cases (2.6%), all intercoccygeal joints were fused. In 11 of these 26 patients (1.1%), fusion was observed in the sacrococcygeal and all intercoccygeal joints. In our study, type II was the most common type of coccyx with intercoccygeal fusion (Table 2).

An investigation was conducted to determine whether there was an increase in fusion rates and the number of coccygeal segments in the entire group. It has been observed that the prevalence of sacrococcygeal and intercoccygeal fusions significantly increases in individuals aged 55 and above. Furthermore, as the number of coccygeal segments increases, fusion rates demonstrate a significant increment ($p<0.001$) (Table 3, Figure-4).

The number of cases with coccygeal spicule was 37 (3.7%) (Fig-2); 21 patients were female, and 16 were male. The coccyx type was type II in 30 of 37 patients (81.1%) (Table 2).

Table 1. Sex distribution of coccyx types and coccygeal segments

Coccyx Type	FEMALE					MALE				
	Number of Coccygeal Segments					Number of Coccygeal Segments				
	2	3	4	5	Total	2	3	4	5	Total
I	4	15	18	2	39	1	13	19	0	33
II	3	85	257	46	391	2	73	196	63	334
III	0	12	71	16	99	0	4	70	20	94
IV	1	4	0	0	5	0	5	0	0	5
Total	8	116	346	64	534	3	95	285	83	466

Table 2. Sex-wise distribution of intercoccygeal fusion, sacrococcygeal fusion, spicules

Type	Sacrococcygeal Fusion			Intercoccygeal Fusion			Coccygeal Spicule		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
I	36	28	64	37	31	68	2	3	5
II	280	222	502	329	280	609	17	13	30
III	64	59	123	78	74	152	2	0	2
IV	4	2	6	4	3	7	0	0	0
Total	384	311	695	448	388	836	21	16	37

Table 3. Sacrococcygeal and intercoccygeal fusion rates according to age and the number of coccygeal segments

	Sacrococcygeal Fusion		p	Intercoccygeal Fusion		p
	-	+		-	+	
Age						
Median (Q1-Q3)	53 (41-66)	58 (43-69)	0.019[U]	54 (41-67)	57 (42-69)	0.294[U]
Mean (SD.)	53.44 (17.46)	56.19 (16.48)		53.99 (17.28)	55.62 (16.73)	
	n (%)	n (%)		n (%)	n (%)	
Age						
≤55	167 (54.8)	315 (45.3)	0.007[c]	87 (53.0)	395 (47.2)	0.200[c]
>55	138 (45.2)	380 (54.7)		77 (47.0)	441 (52.8)	
Type of coccyx						
I	8 (2.6)	64 (9.2)	<0.001[f] <0.001	4 (2.4)	68 (8.1)	<0.007[f] <0.010
II	223 (73.1)	502 (72.2)		116 (70.7)	609 (72.8)	
III	70 (23)	123 (17.7)		41 (25)	152 (18.2	
IV	4 (1.3)	6 (0.9)		3 (1.8)	7(0.8)	
Number of coccygeal segments						
2	3 (1)	8 (1.2)	<0.001[f] ns	3 (1.8)	8 (1)	<0.001[f] ns
3	89 (29.2)	122 (17.6)	<0.001	56 (34.1)	155 (18.5)	<0.001
4	195 (63.9)	436 (62.7)	ns	95 (57.9)	536 (64.1)	ns
5	18 (5.9)	129 (18.6)	<0.001	10 (6.1)	137 (16.4)	<0.001
Number of coccygeal segments						
	3 (0-4)	4 (0-4)	<0.001[U]	3 (0-4)	4 (0-4)	<0.001[U]
	3.7 (4-0.6)	4 (4-0.6)		3.7 (4-0.6)	4 (4-0.6)	

U; Mann Whitney U Test(Monte Carlo), c; Pearson Chi-Square Test(Monte Carlo), f; Fisher Freeman Halton Test (monte Carlo); Post Hoc test: Benjamini-Hochberg correction SD.: Standard Deviation, ns.: Not significant, Q1: 1st quartile, Q3 3th Quartile; +:fusion is present, -: no fusion.

The mean sacrococcygeal straight length was 33.2±7.9 mm in the whole group, 34.3±8.1 mm in males, and 32.2±7.6 mm in females. This length was highest in type IV coccyxes (max 77.5 mm) and shortest in type III (min 11.5 mm). It was also significantly higher in the male group than in the female group (p<0.001, Table 4).

Table 4. Sex-wise distrubution of lateral deviation angle, sacrococcygeal straight length, mean sacrococcygeal and intercoccygeal curvature angles in different coccyx types

Type of Coccyx	Female					Male				
	n	Lateral deviation angle (°)	Sacrococcygeal straight length (mm)	Sacrococcygeal curvature angle (°)	Intercoccygeal curvature angle (°)	n	Lateral deviation angle (°)	Sacrococcygeal straight length (mm)	Sacrococcygeal curvature angle (°)	Intercoccygeal curvature angle (°)
I	39	4.0		0.1	129.6	161.3	33	7.0	31.9	131.7
II	391	5.0	32.6	109.7	145.3	334	6.0	34.4	113.0	144.9
III	99	5.0	31.8	94.9	127.9	94	6.0	34.6	102.7	127.9
IV	5	6.0	22.9	154.8	152.5	5	6.0	34.0	151.6	175.6
Total	534	5.0	32.2	108.8	143.3	466	6.0	34.3	112.7	143.0

The mean sacrococcygeal curvature angle was 110.6±14.9° in the whole group, 108.8±15.4° in the female group, and 112.7±14.2° in the male group. This angle was significantly wider in the male group than in the female group (p<0.001). The largest sacrococcygeal curvature angle (167.2°) was observed in type IV coccyxes, and the smallest sacrococcygeal curvature angle (69.9°) was observed in type III coccyxes (Table 4). The mean intercoccygeal curvature angle was 143.2±19.9° in the whole group, 143.3±20.8° in the female group, and 143.0±18.9° in the male group. The largest intercoccygeal curvature angle (180.0°) was observed in type IV coccyxes, and the smallest angle (76.3°) was observed in type III coccyxes (Table 4).

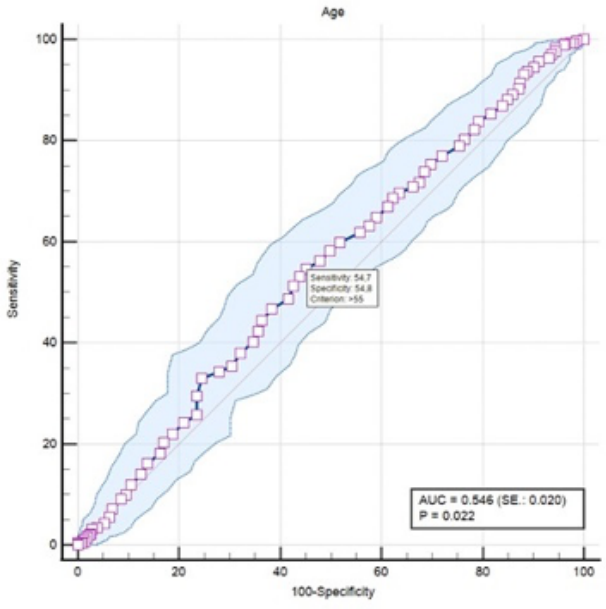

Figure-4; The prevalence of sacrococcygeal and intercoccygeal fusion increases significantly over 55 years of age.

Lateral deviation of the coccyx was observed in a total of 36 cases. A deviation to the right was observed in 21 cases, and a deviation to the left in 15 cases. The lateral deviation to the right was five times more common in the female group than in the male group. Similarly, a lateral deviation on the left side was observed five times more often in the male group than in the female group. This difference was statistically significant (p=0.041). The mean deviation angle was 5.6°; this value was 5.2° in the female group and 6.1° in the male group.

Discussion

Direct radiographs, CT scans, and MRIs can be utilized for the anatomical evaluation of the coccyx. In our study, we preferred 3D CT because we believed that the coccygeal spicule, one of the parameters examined in this study, could be visualized with this modality.

When we analyzed the number of vertebrae in the coccyx, four coccygeal vertebrae were observed in most of the cases. Woon et al. also reported a similar result, but in a study conducted in an Egyptian population, Gebba et al. reported that three vertebrae were observed in most cases [14,17]. Similarly, Przybylski et al. reported that three vertebrae were observed mainly in the Polish population [18]. In a study conducted on Turkish adults, Tetiker et al. reported that the most common number of vertebrae observed was four, which is compatible with our study results [19].

In our study, the most common type of coccyx was type II, and the second most common type was type III. Similar studies in the literature have also revealed that the most common types are type I and type II, respectively [11,12,14,16,19]. In addition, Przybylski reported that type II and type III were the most common in the Polish population, similar to the results in our study [18]. In a study based on pelvic CT scans in a sizeable Korean

population (606 cases), the most common type was also reported as type II coccyx [20].

Regarding sacrococcygeal fusion, 34.3% of our patients had partial fusion, and 35.2% had complete fusion. In total, this rate was 69.5%. There was no significant difference between the male and female groups. Yoon et al. found the rate of sacrococcygeal fusion to be 34% in the Korean population [20]. In the study by Woon et al., sacrococcygeal fusion was reported in more than 50% of the population [16]. Tague stated that the prevalence of sacrococcygeal fusion increased with age [21]. Our study observed that sacrococcygeal and intercoccygeal fusion rates increased significantly over 55 years of age.

This study identified the most common type of sacrococcygeal fusion type II, and the minor joint group was type I. Tetiker et al. have reported the prevalence of sacrococcygeal fusion as 23.8% in males and 21.6% in females. Consistent with our study, a significant increase in the rate of sacrococcygeal fusion was observed with an increase in the number of vertebrae [19].

In our study, intercoccygeal fusion was seen in 836 cases. In 84% of the 836 cases, fusion was observed at the last intercoccygeal joint. Tetiker et al. also reported a similar result [19]. In 26 cases, it was observed that all intercoccygeal joints were fused. In 11 of these 26 cases, fusion was observed in the sacrococcygeal joint and all intercoccygeal joints. These rates are close to the results obtained by Tetiker et al. [19]. In the report published by Woon et al., the rate of intercoccygeal fusion was reported to be 89% [16]. In our study, the most common type of coccyx in which intercoccygeal fusion was observed was type II, and the least common type of coccyx was type IV. As the number of coccygeal vertebrae increased, there was a significant increase in the rate of intercoccygeal fusion.

Coccygeal spicule was present in 3.7% of cases. In the study by Woon et al. [16], this rate was 23%, and Indiran reported it as 8.45% [11]. In the study of Indiran et al., the coccyx types of the patients with coccygeal spicule were mostly Type III and IV [11]. However, in our study, 30 (81.08%) of 37 cases with coccygeal spicule were determined as type II coccyx. The rate of spicule presence was much lower in our study, and the cases with spicule had a type II coccyx, which is a different result than that of other studies.

The mean sacrococcygeal straight length was 33.2±7.9 mm in the whole group, 32.2±7.6 mm in females, and 34.3±8.1 mm in males. This length was greatest in type IV coccyxes and shortest in type III. It was also significantly longer in the male group than in the female group. When studies conducted in different ethnic populations in the literature are examined, it is seen that this length is found to be higher in males than in females [11,14,16].

The mean sacrococcygeal curvature angle was calculated as 110.6±14.9° in the whole group, 108.8±15.4° in the female group, and 112.7±14.2° in the male group. This angle was significantly wider in the male group than in the female group. The largest sacrococcygeal curvature angle was observed in type IV coccyxes, and the smallest was in type III.

The mean intercoccygeal curvature angle was 143.2±19.9° in the whole group, 143.3 ±20.8°in the female group, and 143.0±18.9°in the male group. There was no significant difference between sexes in terms of intercoccygeal curvature angle. The largest intercoccygeal curvature angle was observed in type IV coccyxes, and the smallest was in type III. Both the sacrococcygeal curvature angle and intercoccygeal angles were found to be the highest in type IV coccyxes. The group with the lowest angles was type III.

Although the angles are similar in studies on coccyx morphology in the literature, in a report by Indiran et al., the sacrococcygeal angle was significantly higher in males than in females [11]. In this study, the mean sacrococcygeal angle was found to be 116.69±13.32° in males and 111.66±18.45° in females. In the same study, the intercoccygeal curvature angle was measured as 140.94±19.83° in males and 145.10±19.60° in females. They reported no significant difference between males and females in intercoccygeal angles [11]. Our results on the differences in angles according to sex are consistent with this study.

In the study of Woon et al., no significant male-female difference was observed in terms of

angles. In another study conducted in the Egyptian population, no male-female difference was observed when the mean sacrococcygeal and intercoccygeal angles were compared, similar to the study of Woon et al. [16]. In another study conducted by Yoon et al. in the Korean population, the mean sacrococcygeal angle was found to be 110°. The mean intercoccygeal angle (based on the narrow-angle in the study) was found to be 49° [20]. In a morphometric study of the coccyx conducted by Lee et al. in 136 adult patients using 3D reconstruction CT, as in our study, the authors reported that sacrococcygeal and intercoccygeal angles were found to be higher in females [3].

In our study, lateral deviation of the coccyx was found in 36 cases (20 females, 16 males). Of these cases, 21 were deviated to the right and 15 to the left. The deviation angles ranged from 4–10°. Statistically, there was no difference in deviation angles between males and females.

In the report by Indiran et al., the lateral deviation angle range was found to be 4–11°, and the mean angle was reported as 5.95°. This report stated no difference in the incidence of lateral deviation of the coccyx between males and females, and in 213 cases, lateral deviation of the coccyx was found in 10 patients (seven males, three females) [11]. In the study by Woon et al., the mean deviation angle was reported as 6° [16].

These values are close to our results. In addition, in our study, lateral deviation on the left side was five times more common in the male group than in the female group, and this difference was statistically significant.

Conclusion

There are similarities and differences between different ethnic populations in terms of the morphology of the coccyx. At the same time, in cases with idiopathic coccydynia, whose etiology has not yet been fully clarified, there may be different structural changes according to different ethnic populations. In this sense, this study conducted in asymptomatic individuals can be used as a “set of societal reference values” in future studies on symptomatic individuals to determine the ethnic morphology of the coccyx and the etiology of coccydynia.

Our study has both strengths and limitations. One of the strengths of our study is the high number of participants, which is crucial for ensuring the reliability of the obtained data. Another vital aspect of our study is the comprehensive examination of the subject. The variables analyzed encompassed the Postacchini and Massobrio classification, fusion at the sacrococcygeal and intercoccygeal junction, coccygeal spicule, sacrococcygeal-intercoccygeal curvature angles, and lateral deviation of the coccyx.

In our retrospective study, participants were evaluated solely in a static position using 3D CT scans, and measurements were derived from these static image data. However, the sacrococcygeal and intercoccygeal curvature angles may vary depending on the posture during seated or standing imaging. Further studies incorporating dynamic imaging may be required to obtain more precise data. This limitation should be acknowledged in our study.

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Abbreviation list:

CT; Computed tomography

D; Dimensional

MRI; Magnetic resonance imaging.

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RESEARCH ARTICLE

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Analysis of the Readability of Package Inserts for Attention Deficit Hyperactivity Disorder Medications Used in Turkey

Türkiye'de Kullanılan Dikkat Eksikliği Hiperaktivite Bozukluğu İlaçlarının Prospektüslerinin Okunabilirlik Düzeyi

Pınar Aydoğan Avşar[1], Orhan Kocaman[2]

1.Department of Child and Adolescent Psychiatry, Alanya Training and Research Hospital, Antalya, Türkiye
2.Department of Child and Adolescent Psychiatry, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Türkiye

ABSTRACT

Aim: The readability level of a written text is directly related to how well the text is understood.There are precise formulas that may be used to test readability objectively. The purpose of this research was to evaluate the readability of the ADHD medication package inserts that are presently in use in Turkey.
Methods: 23 medication package inserts for ADHD in total were categorized based on their types. The Turkish Medicines and Medical Devices Agency (https://www.titck.gov.tr/kubkt) provided the most updated package leaflets for the medications in these categories. The Ateşman and Bezirci-Yılmaz readability formulae, which are relevant to Turkish texts, were used to assess package inserts. The Ateşman reading score was calculated to be 72.2 (7-8th grade) on average. The Bezirci-Yılmaz formula has a reading level equivalent to grades 7-8, which corresponds to the primary school level. Based on the 2022 TUIK data in Turkey, it was found that the reading level was suitable for the average education level, except for the SNRI group (high school level).
Conclusion: Given the aforementioned information, we maintain the viewpoint that pharmaceutical package inserts for psychiatric medications ought to ideally contain content written at the level of a primary school (7-8th grade).

Keywords: drug package insert, readability, education level, ADHD

ÖZ

Amaç: Yazılı bir metnin okunabilirlik düzeyi, metnin ne kadar iyi anlaşıldığıyla doğrudan ilişkilidir. Okunabilirliği objektif olarak test etmek için kullanılabilecek kesin formüller vardır. Bu araştırmanın amacı, Türkiye'de halen kullanılmakta olan DEHB ilaç prospektüslerinin okunabilirliğini değerlendirmektir.
Yöntem: Toplam 23 DEHB ilaç prospektüsü türlerine göre kategorize edilmiştir. Türkiye İlaç ve Tıbbi Cihaz Kurumu (https://www.titck.gov.tr/kubkt) websitesinden bu kategorilerdeki ilaçlar için en güncel prospektüsler sağlanmıştır. Türkçe metinlerle için uygulanabilir olan Ateşman ve Bezirci-Yılmaz okunabilirlik formülleri prospektüsleri değerlendirmek için kullanılmıştır. Ateşman okuma puanı ortalama 72,2 (7-8. sınıf) olarak hesaplanmıştır. Benzer şekilde Bezirci-Yılmaz formülü ile de, ilkokul seviyesine karşılık gelen 7-8. sınıflara eşdeğer bir okuma seviyesi tespit edilmiştir. Türkiye 2022 TÜİK verilerine dayanarak, DEHB ilaçlarının prospektüslerinin okunabilirlik düzeyinin, SNRI grubu (lise seviyesi) hariç ortalama eğitim seviyesine uygun olduğu görülmüştür.
Sonuç: Yukarıda belirtilen bilgiler ışığında, psikiyatrik ilaçların ilaç prospektüslerinin ideal olarak ilkokul (7-8. sınıf) düzeyinde yazılmış içerik içermesi gerektiği görüşünü savunuyoruz.

Anahtar Kelimeler: ilaç prospektüsü, okunabilirlik, eğitim düzeyi, DEHB

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*Corresponding Author: Pınar Aydoğan Avşar, MD. Department of Child and Adolescent Psychiatry, Alanya Research and Training Hospital, 07425 Antalya, Turkey. Phone: +90 506 366 70 36 / mail:dr_pinaraydogan@hotmail.com

Orcid: 0000-0001-5938-3243

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Introduction

Readability refers to the degree of simplicity and comprehension a text provides with its writing style. It subsequently establishes a correlation between this metric and the text's level of difficulty to read [1]. An objective method for assessing the readability of a text involves the utilization of a set of mathematical formulas that establish correlations among the word count, syllable count, and sentence length [2], [3]. In recent years, several academic studies have been carried out to evaluate the readability of pharmaceutical package leaflets, patient information forms, and health information websites. These resources are crucial for patients to get accurate information [4].

A patient information leaflet is a technical document included with every drug box and provides written information about the medication. The manufacturer provides patient information leaflets (PILs) that follow a standard structure and provide the same information for each medicine. Their primary goal is educating patients about their drug, including its administration, precautions, and adverse effects. PIL information should be objective, supported by evidence, and written in a style that is easy to read and comprehend for laypeople [5].

Attention-Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in children, with a worldwide incidence of 5.29% and a prevalence of 12.4% in Turkey [6]. The social cost associated with ADHD symptoms and functional impairment emphasizes the significance of regular monitoring in communities. Monitoring ADHD diagnosis, medical treatment receipt, comorbidities, and mortality is critical for timely policymaking in the healthcare system [7]. Adults and children may also suffer the negative impacts of untreated ADHD, If left untreated, ADHD has poorer long-term outcomes [8]. ADHD may result in difficulties in terms of efficiency, social connections, and other psychological health issues. Untreated adult ADHD may also result in complications such as anxiety, sadness, and drug misuse. Notwithstanding the abundance of research, parents and patients have anxieties about the use of ADHD medication. They may be hesitant because they feel some treatments could affect a child's growth. Or they fear a child or adult might get dependent on medication or might need it forever. If parents or patients read a package leaflet without seeking advice from a doctor, they may independently alter the dosage of the medication or discontinue its use. That is why, in the psychiatry field, giving information about the drug's effects and side effects is vital to the content of psychoeducational interventions directed at the patient and their family. Psychotic disorders, now considered neurodevelopmental disorders, are treated with drugs at every stage, but non-compliance with drug therapy is common in these patients, so the physician's duty does not end with drug selection. Previous research indicates that antipsychotic medication noncompliance in schizophrenia and other psychotic diseases ranges from 11% to 80% [9]. The rates of noncompliance with stimulant therapy also range from 20% to 65%, according to studies [10]. As the use of these drugs grows, it is important to make sure that information about them and any bad effects they might cause is easily understandable so that patients are safe and public health is improved. Hence, it is essential that package leaflets be written using uncomplicated and comprehensible language. In the future, they may have the potential to be used as a component of psychoeducation, an essential element of non-pharmacological interventions in the mental health domain. When we look at the studies that have been done on the effectiveness of the medicine package inserts, we find that they are not serving as the main information source for users, not just in our country but also internationally. The purpose of this research was to assess the readability of ADHD medicine package leaflets presently in use in Turkey, as well as to estimate the suitable average age and educational level.

Methods

The author prepared a list of all currently available ADHD medications from the Turkish Drug Guide website [11]. The medications were classified into five groups based on their active ingredients: psychostimulant (methylphenidate), selective noradrenaline reuptake inhibitors (SNRIs- atomoxetine), serotonin-norepinephrine reuptake inhibitors (SSNRIs-venlafaxine),

centrally acting antihypertensive drugs (clonidine, guanfacine), and others (imipramine, bupropion, and modafinil). The Turkish Medicines and Medical Devices Agency (https://www.titck.gov.tr/kubkt) provided the most updated package leaflets for the medications in these categories. By copying, the medicine package insert texts were uploaded to the "https://www.webfx.com/tools/readable/" readability calculation engine. Factors including syllable count, word count, and sentence structure influence the formulae used to objectively quantify readability, which is widely recognized in the scientific community [5]. In 1948, Flesch created the first readability formula that was widely acknowledged in literature [12]. The SPSS version 27 software was used to import the results of these computations Bezirci-Yılmaz and Ateşman's formulae were used to obtain the readability values [2,3].

Ateşman Readability Formula: Readability score =198.825 – 40.175 x word length (total syllables / total words) – 2.610 x sentence length (total words/ total sentences). A readability score ranging from zero to one hundred marks is produced by the above-mentioned formula. Text legibility is classified as "very difficult" (worth 1–29 points), "difficult" (30–49 points), "moderately difficult" (50–69 points), "easy" (70–89 points), or "very easy" (90–100 points) in the evaluation of scores. Alternatively stated, in contrast to the Bezirci-Yılmaz formula, readability improves as the score increases. The points earned may also be used to establish the educational level at which the content is appropriate (Table 1)

The Bezirci–Yılmaz readability formula: Readability score=√OKS x ((H3 x0.84) + (H4x1.5) + (H5x3.5) + (H6x26.25)). This formula, which is based on the number of words in the sentences and the number of syllables in the words, establishes the readability level of the written text in accordance with the Turkish educational system. Higher scores in this formula indicate more complexity in readability (Table 1)

Statistical Analysis

The results of the data obtained in the study were calculated as the mean and standard deviation for continuous variables. Percentage results were calculated for categorical data. The Shapiro-Wilk test was used to determine whether the data were normally distributed. The difference between multiple groups for a continuous variable was examined by One-way ANOVA in the presence of normal distribution, otherwise by the Kruskal Wallis test. Bonferroni correction was made for significance in post-hoc analysis. p-value <0.05 was considered significant. All statistical analysis was performed with SPSS version 27.

Table 1. The level of education that is equivalent to the number of points calculated using the Atesman and Bezirci-Yilmaz readability formula.

ATEŞMAN		Bezirci-Yilmaz	
Score	**Education Level**	**Grade**	**Education Level**
9-100	Primary school 4th grade and below	1-8	Primary school
80-89	5th - 6th grade	9-12	Middle school (High school)
70-79	7th - 8th grade	12-16	Further education
60-69	9th - 10th grade	16+	Academic level education
50-59	11th - 12th grade		
40-49	13th - 15th grade		
30-39	Undergraduate level		
<29	Postrgraduate level		

Results

The research was done using a sample of 23 medicines that are currently used in Turkey for the treatment of ADHD. Out of them, 5 (21.7%) medications were categorized as psychostimulants, 7 (30.4%) were categorized as SNRIs, 3 (13%) were categorized as SSNRIs, 3 (13%) were categorized as centrally acting antihypertensives, and the remaining 5 (21.7%) were grouped under other medications (Table 2). Methylphenidate was in the group of psychostimulants, venlafaxine was in the group of SNRIs, atomoxetine was in the group of SSNRIs, and clonidine and guanfacine were in the group of centrally acting antihypertensives. Imipramine, bupropion and modafinil are classified in the other group.

Based on the assessment conducted by Bezirci

and Yılmaz, it was observed that the reading level of medication inserts belonging to the psychostimulant, SSNRI, and centrally acting antihypertensive groups was equivalent to that of elementary school level.

Table 2. Classification of ADHD medications

		N	%
Pharmaceutical Group	Psychostimulants	5	21,7
	SNRIs	7	30,4
	SSNRIs	3	13,0
	Centrally Acting Antihypertensives	3	13,0
	Other	5	21,7

42.9% of the medication leaflets in the SNRI group had a reading level equivalent to that of elementary school, whereas 57.1% had a readability level equivalent to that of high school.

Within the other group, 40% of the prospectuses were categorized as being at the elementary school level, while the remaining 60% were classified as being at the high school level.

The medication leaflets included in the research did not have a reading level that was at the undergraduate or academic level (Figure 1).

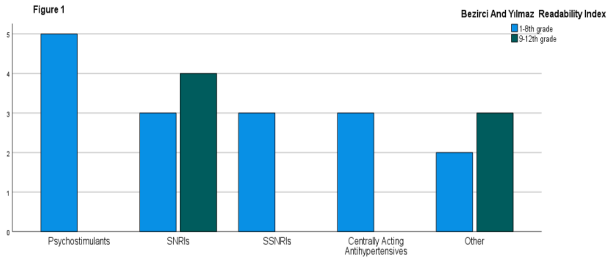

Figure 1. Readability Level of ADHD Medications According to Bezirci-Yılmaz Readability İndex

Based on the Ateşman readability index, the readability of all psychostimulants, SSNRIs, and centrally acting antihypertensive drugs was classified as 7-8th grade. The Ateşman reading score was calculated to be 72.2 on average. Out of the SNRI medication group, the readability of 57.1% of drugs fell into the category of 7-8th grade level, while 42.9% (3) fell into the category of 9-10th grade level. Within the other group, the readability of 40% of the drugs was classified into the category of 7-8th grade level, while 60% were classified as 9-10th grade (Figure 2).

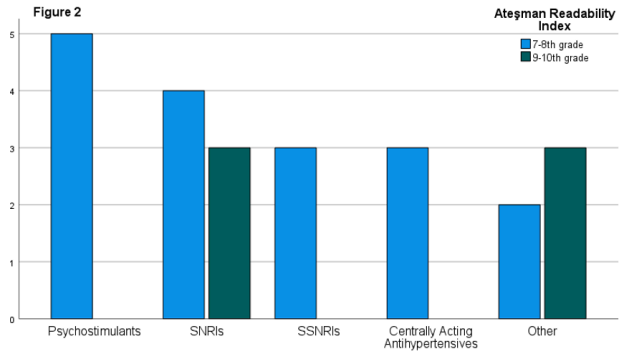

Figure 2. Readability Level of ADHD Medications According to Ateşman Readability İndex

The results of the Ateşman readability formula, the total number of words, and the total number of characters in the prospectuses are given in Table 3. When the drug was compared between groups, no significant difference was detected between the groups for the Ateşman readability index (f (4,18) = 0.771, p = 0.558). When compared in terms of word numbers, a significant difference was found between the groups (H(4) = 10.471, p = 0.033). By using the Bonferroni correction to compare each pair of groups, it was clear that the SNRI group had significantly higher words than the centrally acting antihypertensive group (p = 0.036). Although the comparison between groups revealed a significant difference in terms of the number of characters [H (4) = 9.557, p = 0.049], no significant difference was detected in pairwise comparisons (Table 3).

Discussion

When practicing their art, it is not enough for physicians to simply keep up with the most up-to-date medical information. Precisely informing patients about their medication treatments is a cornerstone deontological principle in medicine that governs patient rights and the effective administration of the treatment process. A medication package insert is a leaflet that comes with a pharmaceutical and gives instructions on how the drug should be taken and what adverse effects patients may suffer [13]. One of the most critical things that affect a patient's ability to adhere to treatment is their level of understanding of the prescription package information [14]. This is maybe more significant in mental health than in other medical specialties. In mental health illnesses, inadequate treatment compliance

Table 3. Comparison of Statistical Data of ADHD Medications' Prospectuses

		Mean ± SD	F /X2	p	Pairwise Comparisons (Adj. Sig.)d
Ateshman Readability Index	1. Psychostimulant	73,86 ±2,87			
	Ateshman	72,47 ±5,39			
	Readability	71,40 ±,529			
	Index	73,53 ±1,02			
	5. Other	69,98 ±3,85	0,771	0,558	
Word Count[c]	1. Psychostimulant	3128,80 ±512,35			
	2 SNRI	5218,71 ±1860,50			1-2(NS), 1-3(NS), 1-4(NS),
	3. SSNRI	3502,33 ±67,84			1-5(NS), 2-3(NS), 2-5(NS),
	4 Centrally Acting Antihypertensive	2051,67 ±371,08			2-4 **(p=0,036)**,
	5. Other	2694,80 ±1095,80	10,471	**0,033**	3-4(NS), 3-5(NS), 4-5(NS)
Character Count[c]	1. Psychostimulant	23981,60 ±3566,85			
	2. SNRI	41213,43 ±15981,27			1-2(NS), 1-3(NS), 1-4(NS),
	3. SSNRI	27330,67 ±533,03			1-5(NS), 2-3(NS),
	4. Centrally Acting Antihypertensive	15990 ±2817,22			2-4(NS), 2-5(NS),
	Character Countc	21517,00 ±8955,30	9,557	**0,049**	3-4(NS), 3-5(NS), 4-5(NS)

c Kruskal-Wallis Test, d Significance values have been adjusted by the Bonferroni correction for multiple tests, NS: Non significant

may impede the patient's capacity to assess reality, which adversely impacts the course of treatment. Despite the crucial role pharmaceutical drug package inserts play in providing health information, there is a scarcity of study on their readability. As far as we know, there has been no research conducted on the readability levels of ADHD medicine package inserts using the Turkish readability method. Our investigation determined that the package inserts of ADHD medicines were written at a basic level (7-8th grade) based on two Turkish readability formulae (Ateşman and Hüseyin-Bezirci). However, in the SNRI group, approximately half of the drug packages were found to have high school-level readability.

In 2011 Haw et al. examined the package inserts of antidepressant medications in the United Kingdom. Approximately 15%, or 5.1 million adults in the United Kingdom, are known to possess the level of literacy expected of children aged 11 or younger [15]. The research assessed the readability, and function of medication package inserts in enhancing patients' understanding and competence in drug use. While the readability ratings of the medicine package inserts were not very low, it was determined that they were inadequate for addressing patients' inquiries about drug use [16]. In another study from 2011, after reading an antidepressant leaflet, participants demonstrated varying levels of comprehension. 45 of the 52 participants held a high school diploma, while seven had completed less than a high school education. It was revealed that only forty percent of the attendees comprehended the material that might be considered significant, and most of them needed help to understand the directions and cautions about serious medical side effects [17]. The other article inspected the drug box inserts of the most commonly used drugs in Iran in 2015, as reported by the Social Security Organization. A

considerable proportion of the medications were identified as having inadequate readability levels, rendering them unsuitable for individuals lacking expertise in reading [18].

In a recent research revealed in Turkey in 2023, it was discovered that the package inserts of antidepressant medications were written at a reading level suitable for students in the 7th and 8th grades, as determined by two Turkish readability formulae [4]. Another Turkish study, carried out in 2021 by Ay and Duranoğlu, assessed the readability of eighty leaflets containing eye drop packages. The study determined that the average level of readability equated to thirteen years of education, or university-level knowledge. Upon examining the mean level of education in Turkey, it becomes evident that it is exceptionally high [19]. An investigation was carried out in Qatar to assess the legibility and understanding of patient information brochures about antidiabetic medications. According to the results, the materials were legible to a minimum of eleventh-grade students, and the majority of patients were incapable of understanding them [20]. A national study evaluated a variety of consent forms obtained from forty-five anesthesia departments by employing a range of readability formulas. The legibility of consent documents obtained from education and research institutions and public hospitals was comparatively low, as indicated by the Gunning Fog index. All institutions exhibited extremely low levels of legibility, as measured by the Flesch-Kincaid index. The Ateşman index revealed that the legibility of consent documents utilized in university hospitals was exceptionally low, while it was also low in other institutions [21].

Jilka S. et al.'s research from 2021 investigated the readability of a smartphone app intended for mental health, with a particular emphasis on depression. The program's readability was found to be in line with the FDA's (Food and Drug Administration) recommended reading level for eighth graders. Nevertheless, as the aforementioned survey also pointed out, the National Adult Literacy Research discovered that more than 25% of American adults struggle to read or understand written material that is beyond the fifth-grade level.

People with lesser levels of education showed a greater frequency of mental problems, according to a 2015 research done in Iran using a population-based methodology and a sample size of 36,000 people [22]. According to the findings of a review study that was carried out in 2007, which was based on earlier research carried out in the United States, fifty percent of hospitalized patients with mental illnesses were identified as being functionally illiterate. The authors advocated using both oral and written information to enhance adherence in patients with depression. They also emphasized the need to present written information in a clear and readily comprehensible manner [23].

The findings of a 2018 national study revealed that the mean educational attainment of the entire populace was 4.8 years for females and 7.1 years for males[24]. According to the information of the Turkish Statistical Institute (TUIK), the average education period in Turkey was 9.2 years in 2022. While the average duration of education received by the population aged 25 and over was 7.3 years in 2011, it increased by 26% to 9.2 years in 2022. The average duration of education for 2022 was 8.5 years for women and 10.0 years for men [25]. According to the “2023 Education at a Glance” report of the Organisation for Economic Co-Operation and Development (OECD), the rate of young people who cannot graduate from high school is higher in Turkey (33%) than the OECD average (14%). While 14.7% of young adults aged 18–24 across OECD countries are in education, employment, or not receiving education, it has been reported that this rate is higher (33.5%) in Turkey [26]. In light of these facts, information on pharmaceutical package inserts for psychiatric drugs, such as ADHD medications, should ideally be written at a primary school (7-8th grade) level. This would significantly improve comprehension and adherence to medical treatment for mental disorders, particularly in our country.

Conclusion

In conclusion, we find that understanding drug interactions with other medications taken simultaneously, as well as how they should be used, work, and cause adverse effects, is essential. It may improve adherence to therapy, which will aid in mental health rehabilitation. Additionally, it would lessen the possibility of legal issues arising

from patient and family misinterpretations of mental health practitioners. It could lessen some repeated admissions of patients. Despite the problem of patient package leaflets being difficult to read is widespread in many countries, some methods may be used to enhance their readability. Public health thus requires the creation and implementation of programs for the syntactic and semantic simplification of these documents.

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ORCID and Author contribution: **P.A.A. (0000-0001-5938-3243** was responsible for formulating the hypothesis, and writing the report, **O.K. (0000-0002-7504-5604)** was responsible for analyses, and writing the report

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RESEARCH ARTICLE

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The Assessment of Bone Metabolism Parameters in Paediatric patients with Genu varum and Genu valgus deformities

Genu varum ve genu valgus deformitesi olan pediatrik hastalarda kemik metabolizmasi parametrelerinin değerlendirilmesi

Hüseyin Kürüm[1*], Şükrü Demir[2], Sefa Key[2]

1.Department of Orthopaedics and Traumatology, Ergani State Hospital, Diyarbakır, Türkiye,
2.Department of Orthopaedics and Traumatology, Faculty of Medicine, Fırat University, Elazığ, Türkiye

ABSTRACT

Aim: There are a limited number of studies in the literature explaining the relationship between bone metabolism parameters such as vitamin D, calcium (Ca), parathormone (PTH), magnesium (Mg), and alkaline phosphatase (ALP) and pediatric lower extremity coronal plane deformities.This study aimed to examine the impact of bone metabolism parameters on the development of genu varum or genu valgus deformities.
Methods: 45 patients with genu varum and genu valgus whose vitamin D, Ca, PTH, Mg and ALP parameters were evaluated in our polyclinic were included in the study.
Results: 44 (97.8%) of the patients were bilateral and one (2.2%) was unilateral. The mean age of patients with genu varum (4.3±4.8) was significantly lower than that of patients with genu valgus (11.9±4.1) (p<0.001). Ca values were normal in 44 (97.8%), vitamin D in 23 (51.1%), PTH in 33 (73.3%), ALP in 2 (4.4%) and Mg in 43 (95.6%) patients. 3% (6.7) of the patients had comorbidities. 2 of these (66.7%) were rickets.
Conclusion: The study shows that ALP can be used as a screening test especially in the coming years. In addition, although there are no sufficient incidence and prevalence studies in the literature, we can say that genu varum is seen more frequently and mostly bilaterally than genu valgus.It is not uncommon for rickets to accompany lower extremity coronal deformities in children. In addition, McCune-Albright Syndrome (MAS) may be accompanied not only by fibrous dysplasia (FD) but also by bilateral genu valgum deformity.

Keywords: Genu varum; genu valgus; bone metabolism parameters.

ÖZ

Amaç: Literatürde D vitamini, kalsiyum (Ca), parathormon (PTH), magnezyum (Mg) ve alkalen fosfataz (ALP) gibi kemik metabolizması parametreleri ile pediatrik alt ektremite koronal plan deformiteleri arasındaki ilişkiyi açıklayan sınırlı sayıda çalışma mevcuttur. Bu çalışmanın amacı, kemik metabolizması parametrelerinin genu varum veya genu valgus deformitelerinin oluşumundaki rolünü araştırmaktır.
Yöntemler: Polikliniğimizde D vitamini, Ca, PTH, Mg ve ALP parametreleri değerlendirilen 45 genu varum ve genu valguslu hasta retrospektif olarak çalışmaya dahil edildi.
Bulgular: Hastaların 44'ü (%97.8) bilateral, biri (%2.2) unilateral idi. Genu varumlu hastaların yaş ortalaması (4.3±4.8) genu valguslu hastalara (11.9±4.1) göre anlamlı derecede düşüktü (p<0.001). Ca değerleri 44 (%97,8), D vitamini 23 (%51,1), PTH 33 (%73,3), ALP 2 (%4,4) ve Mg 43 (%95,6) hastada normaldi. Hastaların 3'ünde (%6,7) ek patoloji vardı. Bunların 2'si (%66,7) raşitizmdi.
Sonuç: Çalışma, ALP'nin özellikle önümüzdeki yıllarda bir tarama testi olarak kullanılabileceğini göstermektedir. Ayrıca literatürde yeterli insidans ve prevalans çalışması olmamakla birlikte genu varumun genu valgusa göre daha sık ve çoğunlukla bilateral olarak görüldüğünü söyleyebiliriz. Riketsin çocuk alt ekstremite koronal deformitelerine eşlik etmesi nadir değildir. Ayrıca McCune-Albright Syndrome (MAS) sendorumuna sadece fibröz displazi (FD) değil bilateral genu valgum deformitesi eşlik edebilir.

Anahtar Kelimeler: Genu varum; genu valgus; kemik metabolizması parametreleri.

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*Corresponding Author: Hüseyin Kürüm, MD. Department of Orthopaedics and Traumatology, Ergani State Hospital, Diyarbakır, Türkiye. Phone: +905313205136 / mail: dr.hsynkrm@gmail.com

ORCID: 0000-0001-9352-2593

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Introduction

Coronal plane angulations of the lower extremities are common in children and are usually physiological. Angular deformities of the lower extremity in the coronal plane have several causes, including abnormal physiological angulation, infection, trauma, skeletal dysplasia, and metabolic disease [1].

Genu varum is the presence of the tibiofemoral axis of the knee joint in the varus, which is normally in 0-6 degree valgus radiographically [2] (figure 1).

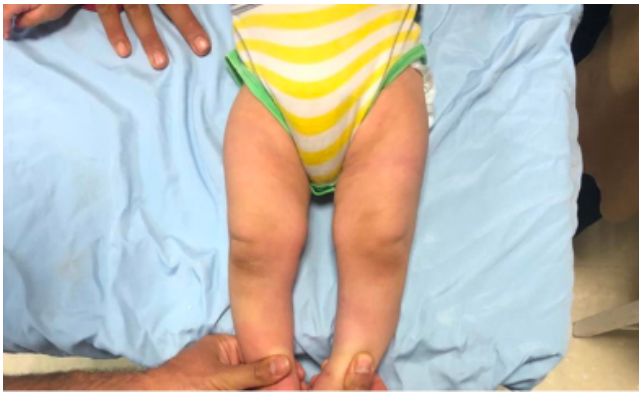

Figure 1. Bilateral genu varum

In common, children acquire an adult valgus alignment of 5-7° by the age of 6 years (figure 2). However, valgus may continue to progress in some [3].

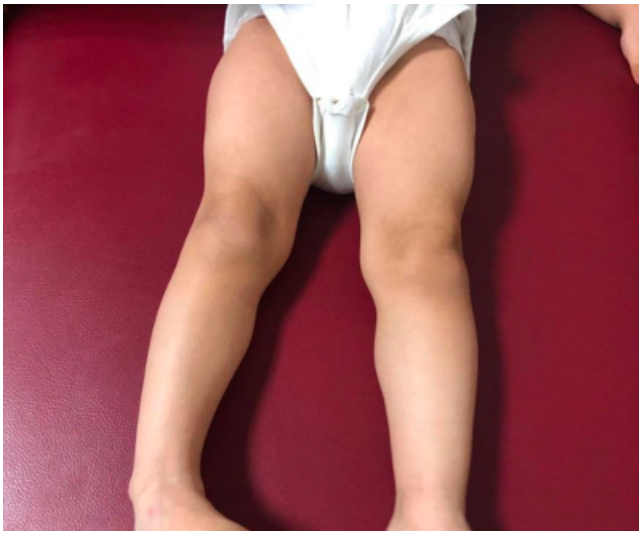

Figure 2. Right genu valgum

The tibiofemoral angle (TFA), mechanical lateral distal femoral angle (mLDFA), and medial proximal tibial angle (mMPTA) are evaluated radiographically in genu varum or valgus. The lateral distal tibial angle (LDTA) should be measured. Mechanical axis deviation (MAD) can be determined by measuring the distance of the mechanical axis from the centre of the knee in millimetres. However, these measurements may not provide accurate results in young patients with deformities and additional evaluations may be required [4].

While evaluating children with genu varum or valgus, bone metabolism parameters should be questioned along with radiographic measurements. Especially vitamin D has an important place in bone metabolism. The enzyme that has a key role in vitamin D synthesis is 1-α-hydroxylase. PTH and Ca are effective in the regulation of this enzyme activity [5].

There are studies showing that insufficient Mg intake increases bone resorption and decreases bone mineral density [6].

In the age group where bone development continues and in cases requiring bone repair, there is an increase in bone ALP activity. Pathologically, primary and secondary hyperparathyroidism, hypo- and hyperthyroidism, primary bone sarcomas and bone metastases are the conditions that increase bone ALP activity the most [7].

Previous studies have established a correlation between vitamin D, Ca, PTH, Mg, and ALP levels and bone metabolism. The significance of these values in various bone disorders has been underscored. Nevertheless, there is a limited number of studies explaining the role of bone metabolism values in the development of lower extremity coronal deformity. In this study, the relationship between serum vitamin D, Ca, PTH, Mg and ALP parameters and deformity development was investigated in children with genu varum and genu valgus admitted to our hospital.

Materials and Methods

A total of 45 patients aged between 18 months and 18 years with genu varum or genu valgus deformity, admitted to the hospital between 2010-2019, years were retrospectively analyzed. All imaging and medical records were extracted from electronic patient records (Picture Archiving and

Communication System—PACS software) in our hospital. Approval for the study was given by the local Ethics Committee (2021/01-04). Data collection and evaluation were done in accordance with the Declaration of Helsinki. All patients were informed about the treatment and their written consent was obtained.

Inclusion criteria

Eligible patients (those with a minimum follow-up of 6 months, under the age of 18, alive at the time of the study, and can be reached through the contact information in the patient file) with genu varum or genu valgus deformity admitted to our outpatient clinic were evaluated. For this purpose , we utilized files, PACS system X-rays, ortorontgenograms, as well as previously analysed serum Ca, vitamin D, PTH, ALP, and Mg values of persons who were admitted to our hospital from October 2010 to November 2019.

Exclusion criteria

Paediatric patients who were inability to stand, with or without support, were excluded from the study due to the incorrect results in X-ray measurements. Furthermore, paediatric patients aged 0-18 months with physiological genu varum and individuals who did not participate in the evaluations 6 months after the initial examination were also excluded from the study.

Diagnosis

Patient diagnoses were determined with the help of history, physical examination findings, laboratory parameters and radiological imaging. In the physical examination of the patients, whether there was gait disturbance, genu varum or genu valgus appearance was determined and recorded. In children older than 7 years of age, direct radiography and ortorontgenogram (figure 3) radiography techniques were used as radiologic imaging.

Radiological evaluation

A diagnosis of genu varum and young valgum was made on the ortorontgenogram. The development of coronal deformity of the lower extremity was evaluated by the average of the MDA values on both sides. Genu varum was defined as an MDA value of at least 11 degrees. Genu valgum was diagnosed as mTFA of 4 degrees or more and the mechanical axis falling lateral to the tibial spine (zones 2 and 3) [8] (figure 3)

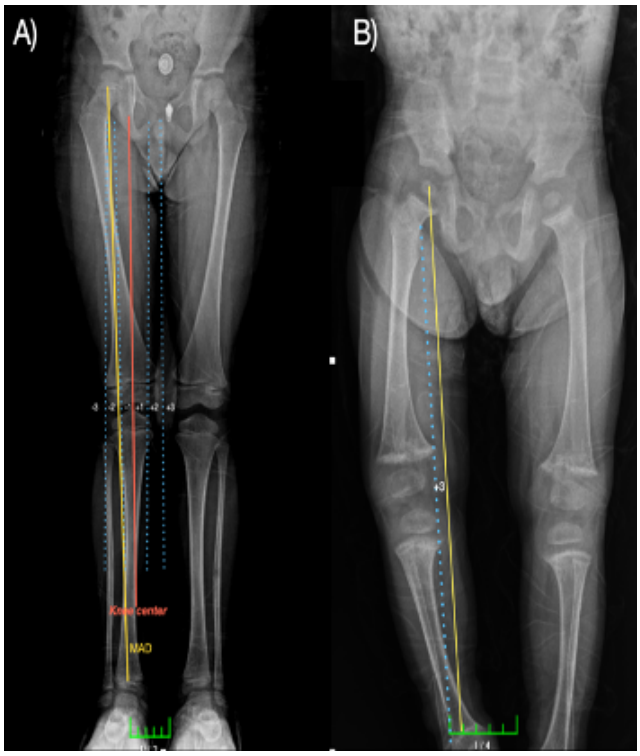

Figure 3. A) Ortorontgenogram image of the right knee of a patient with genu valgum where the mechanical axis deviation (MAD) passes from zone 2. B) Passing of MAD through zone 3 in the knee with genu varum.

Laboratory Measurements

Blood samples were collected from all patients by antecubital venous access using anticoagulant tubes containing EDTA (Ethylenediaminetetraacetic acid).The serum vitamin D, serum Ca, PTH, ALP, Mg values and other routine biochemical tests were performed using an automated analyser (Roche Diagnostic Modular Systems, Rotkreuz, Switzerland). The EDTA anticoagulated blood samples were collected after a 20-minute rest in the morning, stored at 4°C, and analyzed within 30 minutes after sample collection using the Sysmex K-1000 automated analyser (Sysmex, Caribbean, Latin America). The reference range for vitamin D is 25-70 ng/ml, for serum Ca it is 8.5-10.8 mg/dL, for PTH it is 15-65 pg × 109/L, for ALP it is 30-300 U/L and for Mg it is 1.7-2.7 mg/dL.

Statistical Analysis

While evaluating the findings obtained in the study, SPSS (Statistics Package for Social

Sciences) Windows 22.0 was used for statistical analysis. Chi-square analysis was used to compare categorical data. Data were presented as mean±standard deviation, number and percentage. Whether the measurement data are normally distributed was tested with the Shapiro-Wilk test. Student t-test was used to compare the normally distributed pairwise measurement data. Statistical significance was evaluated at the p<0.05 level.

Results

A total of 45 patients, 20 (44.4%) females and 25 (55.6%) males, were included in the study. Genu varum was detected in 36 (80%) and genu valgus in 9 (20%) patients included in the study. There was bilateral involvement in 44 patients (97.8%) and left-sided involvement in 1 patient (2.2%) with genu valgum. Only 3 (6.7%) of these patients had an comorbidity. Of these, 2 (66.7%) had rickets and 1 (33.3%) had MAS (Table 1).

Table 1. Patients' demographic characteristics.

			Total (n=45)
Gender	Female	n(%)	20 (44.4%)
Age (year)			5.8±5.2
Deformity type	Genu Varum	n(%)	36 (80%)
	Genu Valgus		9 (20.%)
Side	Bilateral	n(%)	44 (97.8%)
	Left		1 (2.2%)
Comorbidity	Present	n(%)	3 (6.7%)
	Comorbidity type		2 (66.7%)
			1 (33.3%)
Ca(mg/dl)		mean±SD	9.6±0.7
D vitamin(mcg/L)			19.7±12.3
PTH (pg/mL)			99.8±141.6
ALP(U/L)			361.5±259.4
Mg(mg/dl)			2.1±0.3

Data are expressed as mean±standard deviation (SD) and number (n) (%)

The mean age of patients diagnosed with genu varum (4.3±4.8) was significantly lower than the mean age (11.9±4.1) of patients diagnosed with genu valgus (p<0.001). Bilaterality was observed in 35 (97.2%) of those diagnosed with genu varum and in 9 (100%) of those diagnosed with genu valgus, with no significant difference observed in terms of the side according to the diagnosis (p=0.999). Comorbidity was observed in 1 (2.8%) of those diagnosed with genu varum and in 2 (22.2%) of those diagnosed with genu valgus. There was no significant difference in terms of the presence of comorbidity according to the diagnosis (p=0.097) (Table 2).

Table 2. Comparison of the patients' age, side and comorbidity by diagnosis.

			Genu Varum (n=36)	Genu Valgus (n=9)	p
Age (year)		mean±SD	4.3±4.8	11.9 ±4.1	<0.001
Side	Bilateral	n (%)	35 (97.2%)	9 (100%)	0,999
	Left		1 (2.8%)	-	
Comorbidity	Present		1 (2.8%)	2 (22.2)	0,097
	Absent		35 (97.2)	7 (77.8)	
Ca(mg/dl)		mean±SD	9.6±0.5	9.3 ±1.1	0.180
D vitamin (mcg/L)			20.7 ±13.3	15.9 ±6.5	0.300
PTH(pg/mL)			104.9 ±152.1	79.4 ±92.0	0.634
ALP(U/L)			352.4 ±238.1	397.8 ±346.6	0.644
Mg(mg/dl)			2.1 ±0.3	1.9 ±0.2	0.173

Data are expressed as mean±standard deviation (SD) and number (n) (%)

Vitamin D level was normal in 23 (51.1%) and low in 22 (48.9%) individuals. Vitamin D levels were found to be low in 15 (41.7%) individuals with genu varum and 7 (77.8%) individuals with genu valgum (p<0.071). ALP level was found to be elevated in 43 (95.6%) and normal in 2 (4.4%) individuals. ALP levels were elevated in all individuals with genu valgum deformity and in 34 (94.4%) of those with genu varum deformity (p<0.469). Ca, PTH and Mg levels between individuals are given in Table 3.

Discussion

While bone metabolism aspects perform an important role in the development of juvenile lower extremity coronal plane deformities, paediatric individuals having genu varum and valgum deformity are only followed up in orthopaedics or treated by surgery in cases of deformity progression. However, coronal plane deformities have been associated with many conditions such as rickets [9], genetics, race [10], trauma

and metabolic disease [1] in previous studies. This study established a correlation between bone metabolism parameters and deformities of the lower extremity in the coronal plane. In the study, rickets and MAS were the most frequently observed diseases with coronal plane deformities. Furthermore, the study found that 22 (48.9%) of the patients had a low level of vitamin D. This low vitamin D level was identified as the most significant bone metabolism parameter linked to genu varum and genu valgum deformities.

Table 3. The category of the patient's blood values

		Total	Genu Varum	Genu Valgum	p
Ca	Low	1 (2.2%)	-	1 (11.1%)	0.200
	Normal	44 (97.8%)	36 (100%)	8 (88.9%)	
D vitamin	Low	22 (48.9%)	15 (41.7%)	7 (77.8%)	0.071
	Normal	23 (51.1%)	21 (58.3%)	2 (22.2%)	
PTH	Low	3 (6.7%)	3 (8.3%)	-	0.668
	Normal	33 (73.3%)	26 (72.2%)	7 (77.8%)	
	High	9 (20%)	7 (19.4%)	2 (22.2%)	
ALP	Normal	2 (4.4%)	2 (5.6%)	-	0.469
	High	43 (95.6%)	34 (94.4%)	9 (100%)	
Mg	Low	1 (2.2%)	-	1 (11.1%)	0.364
	Normal	43 (95.6%)	35 (97.2%)	8 (88.9%)	
	High	1 (2.2%)	1 (2.8%)	-	

Generally, from birth to 18 months of age, there is a normal physiological "varus" state in the knee, in which knee varus stays in normal ranges. After the age of two, children normally have increased valgus in their knees, often continuing into adolescence [11]. There are also studies reporting high rates of overweight children [12] and in some races [1]. In the study, it was found that the most of the patients diagnosed with genu varum had genu varum deformity secondary to physiological genu varum and the mean age of the patients diagnosed with genu varum (4.3±4.8) was significantly lower than the mean age of the patients diagnosed with genu valgus (11.9±4.1) ($p< 0.001$). Genu varum was detected in 36 (80%) and genu valgus in 9 (20%) patients included in the study. 44 (97.8%) of the patients had bilateral and 1 (2.2%) had left side involvement. In this study, we concluded that genu varum is more common than genu valgus and is usually bilateral.

Vitamin D has an important place in bone metabolism. Rickets is seen in vitamin D deficiency. Rickets occurs as a result of decreased cartilage and bone mineralization. Rickets is the most common disease among non-communicable conditions in children, and its incidence in our country has been reported in the range of 1.6-19% in different sources [13]. Rickets is an abnormality of the cartilage plates that affects mostly longer bones, causing poor bone development, deficient mineralization and osseous deformities such as knock knees and bow legs. A deficiency of phosphate (PO43-) or calcium ions (Ca2+) is usually a secondary finding as it is essential for normal bone regeneration and mineralization [14] Sakamoto et al. [15] reported that nutritional rickets was commonly observed in individuals with genu varum secondary to physiological genu varum. Ca value in 44 (97.8%) patients was found to be normal vitamin D value in 22 (48.9%) was found to be low in this study. İn this study, 3 (6.7%) of the patients had additional pathology. Only 2 patients had a diagnosis of rickets (66.7%) (Table 1). From the results of this study, it can be concluded that patients with low levels of vitamin D and high levels of ALP are likely to have nutritional rickets. Furthermore, it can be concluded that rickets are commonly associated with genu varum and valgus. As a result, relying on solely orthopaedic treatments is inadequate for the treatment of these deformities necessitating the inclusion of paediatric endocrinology.

Although serum bone ALP levels increase in infancy in both sexes, they tend to increase in proportion to growth rate until puberty [16]. Topak et al. [17] reported that there was no difference in ALP levels between individuals with developmental hip dysplasia and normal individuals. Although ALP is not specifically increased in toddlers solely because of an abnormality of bone metabolism, ALP is thought to be useful for screening for nutritional rickets [18]. Furthermore, recent research has shown a correlation between elevated ALP levels and the worsening of genu varum [19]. Similarly, the ALP level was found to be higher in all paediatric patients in this study. In addition, patients with

severe deformity and additional pathology had higher ALP values compared to others. Therefore, the study suggests that ALP may be used as a future screening test for paediatric lower extremity coronal plane curvatures.

Hyperparathyroidism caused by vitamin D insufficiency is frequently observed in MAS syndrome and can lead to the progression of bone abnormalities [20]. MAS is usually accompanied by fibrous dysplasia which may show monostotic and polyostotic course [21]. Initially, Gorgolini et al. [22] established an association between genu valgum deformity and MAS. In this study, the patient with MAS had bilateral genu valgum deformity.

Kobayashi et al. [23] reported that a low Mg diet reduces the elastic modulus of rat femurs and weakens the femur. Mg deficiency can affect bone directly (by reducing bone stiffness, increasing osteoclasts and reducing osteoblasts) and indirectly (by interacting with PTH and vit D, promoting inflammation/oxidative stress and subsequent bone loss) [24] Shinohara et al. [25] associated various bone metabolic biomarkers such as ALP and Mg with genu varum deformity. In our study, Mg value was normal in 43 (95.6%) of the patients and magnesium levels were not found to be effective in the formation of genu varum or genu valgus. However, studies with larger samples are needed to explain the effect of magnesium on these deformities.

The limitation of the study is that it is a retrospective review without comparing different methods and treatment strategies. Also, long-term follow-up of patients was not performed.

Conclusion

We suggest that bone metabolism parameters should be investigated together with physical examination and radiological evaluation when evaluating paediatric patients with genu varum or genu valgus deformity in the orthopaedic outpatient clinic. The study shows that ALP can be used as a screening test especially in the coming years. In addition, although there are not enough incidence and prevalence studies in the literature, we can say that genu varum is observed more frequently than genu valgus and mostly bilaterally. Rickets frequently occur alongside coronal abnormalities of the lower extremities in children. Furthermore, MAS may be accompanied not only by FD but also by bilateral genu valgum deformity.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Ethics Committee Approval: In this study, national and international ethical rules are observed. The study protocol was approved by the Fırat University Hospital Human Subject Research Ethics Committee (2021/01-04).

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ORCID and Author contribution: **H.K. (0000-0001-9352-2593):** Concept, Design, Supervision, Writing and Critical Review. **Ş.D. (0000-0002-1709-3851):** Literature Search, Resources, analysis and/or interpretation. **S.K. (0000-0003-3620-936X):** Materials, Data Collection and/or Processing, Writing Manuscript.

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RESEARCH ARTICLE

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Comparison of Self-Esteem in Visually Impaired Adults who Participate in Sport and those who do not: A Cross-Sectional Study

Görme Engelli Yetişkinlerde Sporla İlgilenen ve İlgilenmeyen Bireylerin Özsaygı Düzeylerinin Karşılaştırılması: Kesitsel Bir Çalışma

Ayça Aracı[1*], Şehmus Aslan[2], Elif Kabul Gür[3], Ümmühan Baş Aslan[4], Bilge Çalık Başakçı[4]

1.Faculty Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Alanya Aladdin Keykubat University, Alanya, Antalya, Türkiye
2.Faculty Of Sports Sciences, Faculty of Sports Sciences, Pamukkale University, Denizli, Türkiye
3.Faculty Of Health Sciences, Department of Physiotherapy and Rehabilitation, Uşak University, Uşak, Türkiye
4.Faculty of Physiotherapy and Rehabilitation, Pamukkale University, Denizli, Türkiye

ABSTRACT

Aim: Self-esteem is an important psychological concept for mental health. The aim of our study was to compare the levels of self-esteem between visually impaired adults who participate in sports and those who do not.
Method: A total of 85 visually impaired adults were included in the study, including 42 who participate in sports and 43 who do not. A personal information form and the Rosenberg Self-Esteem Scale were used for data collection.
Results: The mean age of the visually impaired adults who participate in sports was 20.86±3.0 years, while it was 20.88±2.92 years for those who do not participate in sports. Among the visually impaired adults who participate in sports, 22 were female and 20 were male, while among those who do not participate in sports, 26 were female and 17 were male. The analysis revealed that the self-esteem of visually impaired adults who participate in sports was statistically significantly higher than that of those who do not participate in sports (p=0.001). It was also observed that the self-esteem of both female and male visually impaired adults who participate in sports was statistically significantly higher than their counterparts who do not participate in sports (female p=0.001, male p=0.020).
Conclusion: It was concluded that participation in sports increases self-esteem in visually impaired adults regardless of gender. In this context, it should be emphasized that participation in sports should be expanded among visually impaired individuals.

Keywords: visual disability, self-esteem, psychological well-being, sports participation, adult

ÖZ

Amaç: Benlik saygısı ruhsal sağlık için önemli bir psikolojik kavramdır. Çalışmamızın amacı, spor yapan ve yapmayan görme engelli bireylerin benlik saygısı düzeylerini karşılaştırmaktır.
Yöntem: Çalışmaya spor yapan 42 ve spor yapmayan 43 olmak üzere toplam 85 görme engelli çalışmaya dahil edildi. Araştırmada bireyler için düzenlenmiş kişisel bilgi formu ve Rosenberg Benlik Saygı Ölçeği kullanıldı.
Bulgu: Spor yapan görme engelli erişkinlerin yaş ortalaması 20.86±3.0 yıl iken, spor yapmayanların 20.88±2.92 yıl idi. Spor yapan görme engelli erişkinlerin 22'si kadın, 20'si erkek iken; spor yapmayanların 26'sı kadın, 17'si erkek idi. Yapılan analiz sonucunda, spor yapan görme engelli erişkinlerin benlik saygılarının yapmayanlara göre istatistiksel açıdan anlamlı düzeyde daha yüksek olduğu (p;0.001) görüldü. Spor yapan hem kadın hem de erkek erişkin görme engelli bireylerin benlik saygılarının spor yapmayan kendi hemcinslerine göre istatistiksel açıdan anlamlı düzeyde daha yüksek olduğu (kadın p;0.001, erkek p;0.020) görüldü.
Sonuç: Spor yapmanın cinsiyetten bağımsız olarak görme engelli erişkinlerde benlik saygısını arttırdığı sonucuna varıldı. Bu bağlamda, görme engelli bireylerde spora katılımın yaygınlaştırılması gerektiği vurgulanmalıdır.

Keywords: Görme engeli, benlik saygısı, psikolojik iyi oluş, spor katılımı, yetişkin

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*Corresponding Author: Ayça Aracı, Faculty Of Health Sciences, Department of Physiotherapy and Rehabilitation, Alanya Aladdin Keykubat University, Alanya, Antalya, Türkiye. mail: uyanayca@gmail.com

Orcid: 0000-0002-1089-3370

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Introduction

"Self" refers to an individual's perceptions and feelings about themselves. Individuals need to ask themselves questions such as: "Who am I?", "What are my goals?", "What is right and wrong?", "What can I do or how should I behave?", "What are my values?", "Should I help others or just think of myself?", to evaluate themselves1 and to understand "Self". To provide logical answers to these questions, individuals need to control their emotions and act rationally. The self develops consciously or unconsciously based on the answers to these questions. To maintain mental health, individuals need to establish a balance between their designed self and their actual self [1].

Self-esteem is expressed through many concepts such as self-respect, self-confidence, self-acceptance, self-worth, self-liking, self-approval, and self-satisfaction [2]. Self-esteem is critical to a successful and satisfying life focusing on feeling psychologically good. Roessler defines self-esteem as the ability to evaluate one's personal progress or regression [3].

On the contrary, people with low self-esteem lack self-respect, self-confidence, easily fall into hopelessness, struggle to fit into society, and tend to develop psychological behaviors against such negativity [1].

For people with disabilities, self-assessment of their abilities in social life is the best measure of self-esteem. Many educators, psychologists, therapists, social workers, and disability sports experts emphasize that skill and success in physical abilities contribute significantly to the development of self-concept.4 The level of self-esteem is negatively affected by the decrease in physical activity; as physical activity decreases, so does self-esteem [5,6].

According to the literature, individuals with high self-esteem are generally more open to active and social relationships, while those with low self-esteem tend to feel weak, inferior, and under pressure in society [7].

Physical activity can improve health, physical fitness, functional independence, and quality of life for both nondisabled and disabled individuals. Proponents of sport and recreation as rehabilitation believe that participation in sport, exercise, and recreational activities increases self-esteem and overall quality of life for both nondisabled and disabled individuals [8]. It has been emphasized that disabled athletes have better social relationships in society compared to non-athletic disabled individuals [9].

The majority of visually impaired people can be passive in interpersonal relationships and have difficulty forming healthy relationships and expressing themselves [10]. Although many researchers have examined behaviors that affect self-esteem and concluded that physical activity contributes positively to self-esteem, the relationship between self-esteem and physical activity remains unclear [11].

Since self-esteem is an important psychological concept for mental health, it important to investigate the effects of sports and exercise on self-esteem in visually impaired individuals. The aim of our study was to investigate the effect of sport on self-esteem in visually impaired people.

Methods

Our study population consisted of members of Denizli Visually Impaired Sports Club. In this club, there are memberships available for 150 visually impaired people, both those who participate in sports and those who do not. The study included visually impaired people between the ages of 18 and 50 who volunteered to participate and who had been physically active for at least two days a week for two years. Participants were unable to walk independently, had diagnosed heart disease, or had hearing, physical, or mental disabilities were not included in the study. All potential participants who met the inclusion and exclusion criteria were verbally informed about the study in a face-to-face interview. In addition, a written document containing details of the study was provided. If the individual volunteered to participate in the study, they were asked to sign an informed consent form. Participants were informed that they were free to withdraw from the study at any time. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, and ethical approval was obtained

from the Pamukkale University Non-Interventional Clinical Research Ethics Board/03,30.01.2018/ 60116787-020/8336.

In the study, a Personal Information Form and the Rosenberg Self-Esteem Scale were used.

Personal Information Form: The Personal Information Form included details such as "age, gender, parental education level, parental employment status, areas requiring assistance, physical activity status, and type of sport in which the individual participates ". Information on participants' medical history and visual acuity was obtained from existing club records. Assessments were conducted via face-to-face interviews by the same researchers

Rosenberg Self-Esteem Scale: The Rosenberg Self-Esteem Scale (RSES) is a self-report test developed by Rosenberg (1965). The validity and reliability of the scale were tested by Çuhadaroğlu (1986). Consisting of 63 items and 12 subscales, this scale includes multiple-choice questions and 4-point Likert-type options. Accordingly, scores range from (0-6), with scores between 0-1 indicating high self-esteem, scores between 2-4 indicating moderate self-esteem, and scores between 5-6 indicating low self-esteem [12,13].

Statistical Analysis: Data were analyzed using the IBM SPSS Statistics 22 software package. Continuous variables were presented as mean ± standard deviation or median (minimum/ maximum), while categorical variables were presented as numbers and percentages. Normal distribution of the data was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was utilized to compare independent group differences. To study the relationship between categorical variables, Chi-Square Test was calculated. Any p value less than 0.05 was considered statistically significant.

Results

Demographic and clinical data of the visually impaired adults are presented in Table 1. Eighty-five visually impaired adults were included in the study. Among the visually impaired adults participating in sports, 22 were female and 20 were male, while among those not participating in sports, 26 were female and 17 were male (Table 1). The mean age of the participants who participate in sports was 20.87±2.94 years, while those not participating in sports had a mean age of 20.88±2.92 years (Table 1).

The analysis revealed that visually impaired adults participating in sports had statistically significantly higher self-esteem compared to those not participating in sports (p=0.001). It was found that the self-esteem of both female and male visually impaired adults participating in sports was statistically significantly higher than that of female and male visually impaired adults not participating in sports (female p=0.001, male p=0.020) (Table 2).

Discussion

In this study, we compared self-esteem levels of visually impaired adults who participate in sports with those who do not, and we found that participating in sports increased self-esteem in both male and female visually impaired adults. As visual impairment decreases, self-esteem and social interactions are reported to increase [14]. However, the level of visual impairment of the individuals was not measured in this study. We are interested in studying the impact of sports participation on self-esteem. In this regard, the literature reports that participation in sports, exercise, and recreational activities increases self-esteem in disabled veterans [9].

Similar to our study, a dissertation study by Uygun (2016) compared the differences in self-design among 40 visually impaired individuals based on whether they participated in sports or not, and found that visually impaired students who participated in sports had better self-designs [15].

In our study comparing the self-esteem of visually impaired adults who participate in sports with those who do not, we found that visually impaired individuals who participate in sports have higher self-esteem than those who do not. Gençay and Özcan (2019) compared the self-esteem and life satisfaction of visually impaired people who participate in sports and concluded that as the self-esteem of visually impaired people who participate in sports increases, so does their life satisfaction. Based on this, it can be assumed

Table 1. Demographics of Visually Impaired Adults

	Sports Participants (n:42)	Non-Sports Participants (n:43)	p
Age (Years) (Mean±SD)	20.86±3.0	20.88±2.92	0.915**
	n(%)	n(%)	
Gender (Female/Male)	22(52.4)/20(47.6)	26(60.5)/17(39.5)	0.452*
Father's Education Level			0.232*
-Illiterate	3(7.1)	1(2.3)	
-Literate	1(2.4)	4(9.3)	
-Primary School	10(23.8)	14(32.6)	
-Secondary School	5(11.9)	9(20.9)	
-High School	14(33.3)	12(27.9)	
-University	9(21.4)	3(7.0)	
Mother's Education Level			0.831*
-Illiterate	3(7.1)	4(9.3)	
-Literate	3(7.1)	7(16.3)	
-Primary School	12(28.6)	13(30.2)	
-Secondary School	11(26.2)	10(23.3)	
-High School	7(16.7)	5(11.6)	
-University	6(14.3)	4(9.4)	
Father's Occupation -Not working	5(11.9)	4(9.3)	0.697*
-Working	37(88.1)	39(90.7)	
Mother's Occupation -Not working	17(40.5)	21(48.8)	0.438*
-Working	25(59.5)	22(51.2)	
Duration of Disability -Since birth	23(54.8)	34(79.1)	0.022*
-Acquired later	19(45.2)	8(18.6)	
Need for Assistance			
-Eating -Yes	-	1(2.3)	0.320*
-No	42(100)	42(97.7)	
-Meal Preparation -Yes	1(2.4)	1(2.3)	0.987*
-No	41(97.6)	42(97.7)	
- Dressing/Undressing -Yes	-	-	-
-No	42(100)	43(100)	
-Bathing -Yes	-	1(2.3)	0.320*
-No	42(100)	42(97.7)	
-Shaving -Yes	-	2(4.7)	0.157*
-No	42(100)	41(95.3)	
-Hair Combing -Yes	-	-	0.309*
-No	42(100)	43(100)	
Sport Discipline			
-Futsal	10(23.8)		
-Goalball	7(16.7)		
-Chess	9(21.4)		
-Athletics	9(21.4)		
-Football	3(7.1)		
-Swimming	4(9.5)		

**Mann Whitney U Test, *Chi-Square Test,

that sports may have a positive effect on the self-esteem of visually impaired people and related psychosocial factors [16].

Dalbudak and Yiğit (2019) evaluated self-esteem based on whether hearing-impaired people participate in sports, they found no difference in self-esteem scores [17]. Saygılı et al. (2015) observed in their study that there was no difference in self-esteem scores based on sports participation [18]. In this sense, our study shows that there is a significant relationship between sports participation and self-esteem, contrary to the literature.

Table 2. Intergroup comparison results of visually impaired adults

	Rosenberg Self-Esteem Scale			
Variables	n	Mean±SD	Min/Max	p*
Sports participants	42	25.97 ±4.06	10/30	0.001
Non-sports participants	43	19.86 ±6.27	4/10	
Female sports participants	22	28.00 ±3.45	18/30	0.001
Female non-sports participants	26	20.50 ±6.24	7/30	
Male sports participants	20	25.00 ±4.54	10/30	0.020
Male non-sports participants	17	22.00 ±6.42	4/27	

* Mann Whitney U test, $p^*<0.05$

Augestad (2017) reviewed publications evaluating self-esteem in visually impaired children and young adolescents conducted in 15 different countries between 1998 and 2016 [14]. It was noted that only 7 of the publications included in the study had more than 100 participants, indicating a small sample size. Of the 26 publications they reviewed, 5 found that the self-esteem of visually impaired children was low or very low compared to non-disabled children [15]. No significant differences were found in 7 publications. Some of these publications emphasized positive differences in favor of visually impaired children. Some studies have found differences by age group. The significant differences found in the study results were related to the impact of disability severity on self-esteem. In this regard, two studies found that the severity of visual impairment did not affect self-esteem, whereas four other studies found the opposite [19,20]. The level of visual impairment was not specified in our study. However, it was observed that exercise in particular had a positive effect on the self-esteem of visually impaired people. As emphasized in the literature, exercise is seen as a method and tool to reduce the negative effects of disability on personal development for people with disabilities [10,21,22]. Exercise is seen as a method and tool to reduce the negative effects of disability on personal development for people with disabilities [8].

High levels of physical activity with health benefits are possible for children and adolescents with visual impairments. According to the World Health Organization (WHO), physical inactivity is a major health problem [23]. The education system, the sports system, and society in general do not pay enough attention to people with disabilities. Therefore, it is increasingly recognized that the problem does not lie with the disabled individual, but rather with the structures, practices, and attitudes that prevent individuals from using their abilities [23].

Limitations

The main limitation of our study is the small sample size. The secondary limitation is that the individuals included in our study have a specific age range. However, the fact that this is a cross-sectional study, the the maximum number of visually impaired people were reached in the province where the study was conducted constituted a small population, and that visually impaired people participating in sports were part of this population, caused the population of our study to be a more isolated group.

It is recommended that further studies be conducted with a larger sample size evaluating more parameters.

Conclusion

In the light of the information obtained from the study, it can be said that visually impaired people find peace with themselves and experience positive emotions in life by participating in sports. It is therefore concluded that sport plays a significant role in this regard. The positive impact of sport on people with disabilities has been demonstrated. Self-esteem affects the quality of an individual's life, and to improve the self-esteem

of visually impaired people, it is recommended that they be encouraged to participate in sports and recreational activities that allow them to lead an active life.

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ORCID and Author contribution: A.A. (0000-0002-1089-3370): Conception, Materials, Analysis and/or Interpretation, Writing. **Ş.A. (0000-0003-4685-2957):** Design, Conception, Materials, Analysis and/or Interpretation, Writing. **E.G.K. (0000-0003-3209-1499):** Statistic, Processing, Literature Review, Writing. **U.B.A. (0000-0001-6483-503x):** Supervision, Resource, Writer, Critical Review. **B.B.Ç. (0000-0002-7267-7622**): Supervision, Resource, Writer, Critical Review.

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The Impact of Prolotherapy and Steroid Injection on De Quervain's Tenosynovitis: A Retrospective Outcome Study

Proloterapi ve Steroid Enjeksiyonunun De Quervain Tenosinoviti Üzerindeki Etkisi: Retrospektif Sonuç Araştırması

Hakan Zora[1], Gökhan Bayrak[2]*

1Department of Orthopedics and Traumatology, Private Medicabil Hospital, Nilüfer/Bursa, Türkiye
2Department of Physiotherapy and Rehabilitation of the Faculty of Health Sciences, Muş Alparslan University, Muş, Türkiye

ABSTRACT

Aim: Patients with De Quervain's stenosing tenosynovitis (DQT) experience problems in daily living activities due to the chronic inflammatory process and tenderness around the wrist. This study aimed to compare the effects of prolotherapy and steroid injection on short-term functional outcomes in DQT patients.
Methods: In this retrospective study between January 2022 and 2023, a cohort of 34 patients with complete demographic data and elbow pain and functional scores, which were recorded at pre-treatment, two weeks, and six weeks post-treatment, was divided into the steroid injection (n=17) and prolotherapy (n=17) groups. Demographic and clinical data of all patients were recorded. The outcomes of the Visual Analogue Scale (VAS) score for wrist pain, Quick Disability Assessment of Arm, Shoulder, and Hand Problems (QuickDASH), and the Health Assessment Questionnaire (HAQ) for wrist functions were examined.
Results: Initial assessments did not reveal any differences between groups in terms of VAS (p=0.756), QuickDASH (p=0.168), and HAQ (p=0.615). In the second week post-treatment, there was a significant reduction in VAS, QuickDASH, and HAQ in steroid injection compared to the prolotherapy (p=0.001). This difference continued at sixth-week post-treatment; VAS (p=0.007), QuickDASH (p=0.003), and HAQ (p=0.011) were found to be significantly lower in steroid injection than in the prolotherapy.
Conclusion:Our findings underscore the superior effectiveness of steroid injection compared to prolotherapy in reducing wrist pain and improving functional outcomes in patients with DQT. These findings benefit orthopedic settings in choosing treatment options logically, though further research is needed to understand long-term effects and mechanisms.

Keywords: De Quervain stenosing tenosynovitis, injections, steroids, prolotherapy

ÖZ

Amaç: De Quervain stenozan tenosinovitli (DQT) hastalar, kronik inflamatuar süreç ve el bileği çevresindeki hassasiyet nedeniyle günlük yaşam aktivitelerinde problemler yaşamaktadır. Bu çalışmanın amacı DQT hastalarında proloterapi ve steroid enjeksiyonunun kısa dönem fonksiyonel sonuçlar üzerindeki etkilerini karşılaştırmaktır.
Yöntem: Ocak 2022-2023 tarihleri arasında yapılan bu retrospektif çalışmada demografik verileri eksiksiz olan ve tedavi öncesi, tedavi sonrası iki hafta ve altı hafta dirsek ağrısı ve fonksiyonel skorları kaydedilen 34 hastadan oluşan bir kohort steroid enjeksiyonu (n=17) ve proloterapi (n=17) gruplarına ayrıldı. Tüm hastaların demografik ve klinik verileri kaydedildi. El bileği ağrısı için Görsel Analog Skalası (GAS) skoru, el bileği fonksiyonları için Kol, Omuz ve El Problemlerinin Hızlı Engellilik Değerlendirmesi (QuickDASH) ve Sağlık Değerlendirme Anketi (SDA) sonuçları incelendi.
Bulgular: İlk değerlendirmelerde GAS (p=0,756), QuickDASH (p=0,168) ve SDA (p=0,615) açısından gruplar arasında fark yoktu. Tedavi sonrası ikinci haftada, steroid enjeksiyonunda proloterapiye kıyasla GAS, QuickDASH ve SDA'da anlamlı bir azalma görüldü (p=0,001). Bu fark tedavi sonrası altıncı haftada da devam etti; GAS (p=0,007), QuickDASH (p=0,003) ve SDA (p=0,011) steroid enjeksiyonunda proloterapiye göre anlamlı şekilde düşük bulundu.
Sonuç: Elde edilen bulgular DQT'li hastalarda steroid enjeksiyonunun proloterapiye kıyasla el bileği ağrısını azaltmada ve fonksiyonel sonuçları iyileştirmedeki üstün etkinliğinin altını çizmektedir. Bu bulgular, tedavi seçeneklerinin mantıklı bir şekilde seçilmesinde ortopedik çerçeveye fayda sağlamaktadır, ancak uzun vadeli etkileri ve mekanizmaları anlamak için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: De Quervain stenozan tenosinoviti, enjeksiyonlar, steroidler, proloterapi

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*Corresponding Author: Gökhan Bayrak, PhD. Department of Physiotherapy and Rehabilitation of the Faculty of Health Sciences, Muş Alparslan University, 49250, Muş, Türkiye. Phone: +905356291670 / mail: gokhan2803@gmail.com

ORCID: 0000-0001-9224-996X

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Introduction

De Quervain's stenosing tenosynovitis (DQT) presents a distressing tendinosis characterized by discomfort and tenderness surrounding the radial styloid of the wrist during routine activities necessitating wrist and thumb motions.[1] Various potential etiologies for DQT have been postulated thus far, encompassing direct trauma, biomechanical compression, excessive fatigue from repetitive activities, genetic predisposition, as well as exposure to cold and heat; nevertheless, the precise causative factor remains a subject of contention.[2] DQT primarily originates from inflammation of the abductor pollicis longus (APL) tendons and extensor pollicis brevis (EPB).[3] With prevalence rates of 0.5% in men and 1.3% in women, DQT predominantly affects individuals within the age bracket of 40-60 years.[2] DQT usually affects especially adults who use repetitive hand or wrist movements in their daily activities. However, it can also arise in men and women who play sports or use hand instruments to strain the tendons in the wrist and hand.[3]

The management of DQT poses a considerable challenge for patients, with current conservative approaches encompassing a spectrum of interventions. These include pharmacotherapy involving oral nonsteroidal anti-inflammatory drugs, local corticosteroid injections, rest splints, prolotherapy, platelet-rich plasma, tailored physiotherapy regimens, and physical modalities.[2,4] Alternative conservative strategies other than steroid injections, though available, show limited efficacy and are associated with a notable recurrence rate.[1] Steroid injections are widely accepted for DQT, and their effectiveness has been demonstrated in previous reports and systematic analyses.[1,5] Nonetheless, the existing body of evidence in the form of systematic reviews and meta-analyses regarding steroid injection therapy for DQT remains limited.[5]

Prolotherapy, a therapeutic modality entailing the administration of sclerosing agents around painful tendinosis, has garnered increasing attention in upper extremity pathologies, as evidenced by a growing body of literature.[6] Despite this burgeoning interest, exploring prolotherapy's efficacy in addressing DQT remains limited, with only two case studies thus far delving into its potential benefits. These studies have suggested that prolotherapy exhibits comparable efficacy to steroid injection in mitigating pain and offers favorable prognostic outcomes for symptom alleviation among DQT patients.[7,8] However, more research is needed regarding the comparative short-term effects of prolotherapy versus steroid injection on wrist pain and functional outcomes in individuals afflicted with DQT. Therefore, this study aimed to compare prolotherapy and steroid injections on wrist pain and functional outcomes in DQT patients.

Methods

The study was designed as a retrospective analysis, wherein we examined the records of 38 patients diagnosed with DQT who sought treatment for wrist pain at a Bursa Private Medicabil Hospital's orthopedics and traumatology polyclinics experiencing wrist pain for at least four weeks. All patients had been treated with either prolotherapy or steroid injections between January 2022 and January 2023. Ethics committee approval of the study was obtained from the Muş Alparslan University Scientific Research and Publication Ethics Committee (134645-5/53). The study was performed following the ethical standards of Helsinki. The informed consent form was obtained from all patients.

A cohort of 34 patients, characterized by complete demographic data, elbow pain, and functional scores recorded at pre-treatment, two weeks, and six weeks post-treatment, was divided into the steroid injection (n=17) and prolotherapy (n=17) groups. Patients experiencing wrist pain for at least four weeks and showing no improvement with thumb-supported static hand-wrist splinting and nonsteroidal anti-inflammatory drugs for a minimum of three weeks were included. Inclusion criteria were at least 40 mm pain according to the Visual Analogue Scale (VAS) around the distal of the radial styloid process, non-responsiveness to nonsteroidal anti-inflammatory medications and thumb-supported static hand-wrist splinting over three weeks, tenderness on the first dorsal compartment of the wrist, positive Finkelstein's sign, ineffectiveness of oral medication in

ameliorating the condition, and ages ranging from 18 to 65 years. Exclusion criteria encompassed patients who had undergone multiple steroid injections in the preceding six months, those with contraindications to steroid therapy, individuals with predisposing factors such as past fractures/ dislocations, rheumatoid arthritis, or prior surgery in the same wrist region, as well as pregnant individuals and those with cancer, as these conditions could potentially confound functional outcome assessments.

Each patient enrolled in the study received comprehensive instruction in a standardized physiotherapy regimen, which included specific exercises targeting the APL and EPB muscles, performed twice to thrice daily.[9] Additionally, a friction massage regimen and 5 to 10 minutes of cold application per/day were administered every three days, following the previous protocol.]10] All patients were given information and a follow-up chart as a home exercise program. Notably, all participants were instructed to use a thumb-supported static hand-wrist splint for six weeks following prolotherapy or steroid injections and to avoid strenuous physical activities involving the hand and thumb. Before the prolotherapy and steroid injection, the skin was stained with sterile povidone-iodine and ethyl alcohol. Approximately 0.5 cm distal to the radial styloid was marked with the patient sitting with the elbow flexed 90 degrees and the forearm neutral. For the steroid injection, a 22-gauge needle linked to a 5cc syringe constituting 1 ml of Methylprednisolone (40mg/ml) plus 1 ml of 0.5% lignocaine was prepared and injected into the tendon sheath. [11] In the prolotherapy group, injection with a 4ml mixture of 1% lidocaine and 12.5% dextrose was administered distal to the radial styloid and tendon sheath with a 22-gauge needle.[7] After the prolotherapy and steroid injections, the ice application was accomplished at the affected site.

Evaluations: Demographic data of all patients were recorded. The VAS is used to evaluate wrist pain, and the Quick Disability Assessment of Arm, Shoulder, and Hand Problems (QuickDASH) and the Health Assessment Questionnaire (HAQ) are used to evaluate wrist function. The previously recorded VAS, QuickDASH, and HAQ scores were examined. Patients with before injection, two weeks after, and sixth-weeks outcome were complete were included in the study.

Visual Analogue Scale: The VAS is one of the most commonly used scales for assessing adult pain. In our study, all patients were asked to mark the severity of their activity pain on a 100 mm VAS, and the marked part was recorded in mm. [12]

Quick Disability Assessment of Arm, Shoulder, and Hand Problems: The QuickDASH is a Likert-type scale to evaluate physical function in patients with upper extremity musculoskeletal disorders. QuickDASH consists of 11 items, with questions scored from 1 to 5. A score of 1 indicates no strain, and a score of 5 indicates inability to perform the selected activity. The total score of the QuickDASH ranges from 0 to 100 (0 points indicate no impairment and 100 points indicate severe impairment). Lower scores obtained from QuickDASH indicate a better functional level for patients.[13]

Health Assessment Questionnaire: The HAQ is a comprehensive scale for evaluating various aspects of a patient's physical functioning over the past week. It meticulously assesses upper extremity movements, lower extremity locomotor activities, and tasks involving both upper and lower extremities. Comprising 20 questions organized into eight distinct subcategories, including dressing, standing up, eating, walking, hygiene, reaching, grasping, and daily tasks, the HAQ employs a scoring system ranging from 0 to 3. A score of 0 signifies no difficulty, while a score of 3 indicates the inability to perform the activity. The total score is derived by summing the scores of the marked items and dividing by the number of items marked. Typically, scores between 0 and 1 suggest mild to moderate difficulty, while those between 1 and 2 indicate moderate to severe disability, and scores between 2 and 3 denote severe disability.[14]

Statistical Analysis: The statistical analysis of the data obtained was conducted using the SPSS program, specifically Version 25, developed by IBM in Armonk, NY, USA. Descriptive statistics were utilized to present the data, and mean and standard deviation were reported. The analysis of variance test (ANOVA) was employed for comparisons between groups with normally

distributed data, while the Kruskal-Wallis analysis was utilized for non-normally distributed data. In cases of repeated measurements, the repeated measures ANOVA test was applied. The statistical significance was set at $p<0.05$.

Results

Upon analyzing the demographic data, no significant differences were observed between the groups in age (p=0.552) and body mass index (p=0.755). In the steroid injection and prolotherapy cohorts, 52.9% (n=9) of patients were female, whereas 47.1% (n=8) were male. 88.2% (n=15) of patients in the prolotherapy group showed dominant limb involvement, with the remaining 11.8% (n=2) experiencing non-dominant limb involvement. In contrast, in the steroid injection group, 82.4% (n=14) of patients reported affected dominant limbs, while 17.6% (n=3) presented with non-dominant limb involvement (Table 1).

Table 1. Demographic and clinical data of the groups

	Prolotherapy (n=17)		Steroid Injection (n=17)		
	Mean ± SD	%95 CI	Mean ± SD	%95 CI	p
Age (year)	37.58 ± 7.20	33.88 – 41.29	36.17 ± 6.45	32.85 – 39.49	0.552 (t=0.602)
Body mass index (kg/m2)	23.26 ± 2.13	22.16 – 24.36	23.51 ± 2.42	22.26 – 24.75	0.755 (t=-0.315)
	n	%	n	%	
Sex					
Female	9	52.9	9	52.9	1.000
Male	8	47.1	8	47.1	
Dominant Extremity					
Right	16	94.1	15	88.2	0.545
Left	1	5.9	2	11.8	
Affected Extremity					
Dominant	15	88.2	14	82.4	0.628
Non-dominant	2	11.8	3	17.6	

SD: standard deviation; kg: kilogram; m: meter; t: independent samples t-test, %95 CI: %95 Confidence Interval for means

Initial assessments did not reveal differences between the groups before beginning the treatment in wrist pain (VAS, p=0.756) and functional capacity (QuickDASH, p=0.168; HAQ, p=0.615). However, after two weeks of post-treatment, there was a significant reduction in both wrist pain and functional abilities in the steroid injection group compared to the prolotherapy group (p=0.001). This difference continued to persist at the six-week follow-up, with wrist pain (VAS, p=0.007) and functional abilities (QuickDASH, p=0.003; HAQ, p=0.011) being notably lower in the steroid injection group than in the prolotherapy group (Table 2).

Table 2. Intragroup and intergroup comparisons of wrist pain and function in prolotherapy and steroid injection groups

	Prolotherapy (n=17)		Steroid Injection (n=17)		
	Mean ± SD	%95 CI	Mean ± SD	%95 CI	P1
VAS (mm)					
Before	79.64 ± 7.01	76.04 – 83.25	80.47 ± 8.26	76.22 – 84.71	0.756 (F=0.098)
2nd week	17.41 ± 6.66	13.98 – 20.83	8.94 ± 4.53	6.61 – 11.27	0.001* (F=18.783)
6th week	10.47 ± 6.83	6.95 – 13.98	5.17 ± 3.39	3.43 – 6.92	0.007* (F=8.174)
P2	0.001*1-2, 1-3, 2-3 (η^2=0.155)				
QuickDASH					
Before	46.92 ± 8.83	42.37 – 51.46	51.73 ± 10.15	46.51 – 56.95	0.150 (F=2.174)
2nd week	20.31 ± 8.29	16.05 – 24.57	6.27 ± 3.26	4.59 – 7.95	0.001* (F=42.214)
6th week	7.21 ± 5.97	4.14 – 10.28	2.27 ± 1.96	1.25 – 3.28	0.003* (F=10.520)
P2	0.001*1-2, 1-3, 2-3 (η^2=0.340)				
HAQ					
Before	1.13 ± 0.11	1.07 – 1.19	1.11 ± 0.12	1.05 – 1.17	0.615 (F=0.258)
2nd week	0.46 ± 0.22	0.35 – 0.58	0.19 ± 0.11	0.13 – 0.25	0.001* (F=20.785)
6th week	0.22 ± 0.17	0.13 – 0.31	0.10 ± 0.07	0.06 – 0.13	0.011* (F=7.321)
P2	0.001*1-2, 1-3, 2-3 (η^2=0.224)				

SD: Standard deviation; %95 CI: %95 Confidence Interval for means; mm: millimeters; VAS: Visual Analogue Scale; QucikDASH: Quick Disability Assessment of Arm, Shoulder, and Hand Problems; HAQ: Health Assessment Questionnaire; η2: Eta square analysis for effect size
P1: p-value for the difference between independent groups
P2: p-value for difference in dependent groups

In the sixth week following injections, the VAS wrist pain level exhibited a change of 75.29±8.42 mm in the steroid injection group and 69.17±10.61 mm in the prolotherapy group (Figure 1). Regarding the QuickDASH wrist function score, a change of 49.46±10.37 points was observed in the steroid injection group compared to 39.70±11.25 points in the prolotherapy group (Figure 2). Additionally,

the change in HAQ score amounted to 1.01±0.09 points in the steroid injection group and 0.91±0.22 points in the prolotherapy group (Figure 3).

Discussion

In this study, which aimed to compare the effects of steroid injection or prolotherapy on short-term wrist pain and functions in patients with DQT, the steroid injection group experienced greater improvements in both wrist pain levels and functional abilities at the six-week follow-up compared to the prolotherapy group in the short-term follow-up.

Pain experienced by patients with DQT predominantly arises from resistance encountered by the APL and EPB tendons within the thickened compartment.[15] Among the conservative treatment options for DQT pain relief, steroid injection therapy consistently emerges as the most effective method in various studies.[5,16] Likewise, prior meta-analyses have indicated that steroid injections have shown superiority in alleviating pain in the short term among DQT patients.[17,18] While there is limited evidence to support the treatment of DQT, prolotherapy has become increasingly popular in recent years. Prolotherapy inhibits capsaicin-sensitive receptors and calcitonin gene-related peptides, contributing to nerve and tissue inflammation and edema. This helps to reduce neurogenic inflammation.[15] Additionally, prolotherapy functions as a nutrient at the injection site, prompting the body's natural tissue repair processes,[8] with reported pain improvement ranging from 70% to 80%.[15] Prior research has reported the efficacy of physiotherapeutic interventions, including APL and EPB strengthening, cryotherapy, and manual massage therapy, in reducing pain among patients with DQT.[9,10,19] In this investigation, we consider that the physiotherapy regimen administered to both injection groups might potentially support steroid and prolotherapy injections to reduce pain levels. The findings regarding pain in this study align with previous observations, supporting the short-term efficacy of steroid injections over prolotherapy in alleviating pain among DQT patients. The findings of this study align with previous observations, supporting the short-term efficacy of steroid injections over prolotherapy in alleviating pain among DQT patients.

Interventional injection techniques, such as steroid injection or prolotherapy, are often pursued when conservative treatment modalities fail to address conditions such as DQT adequately.[8] However, a paucity of literature exists concerning the assessment of functional outcomes after such injections in DQT patients. Noteworthy studies include Vaghasia et al.'s findings of an 80% functional improvement following prolotherapy injections for DQT,[15] and Rowland et al.'s observations of functional enhancement based on DASH scores post-steroid injections.[17] Furthermore, Bhat et al. discovered comparable pain relief and functional outcomes between ultrasound-guided steroid injections and surgical release.[1] The systematic reviews conducted by Cavaleri et al. and Calloumas et al. highlighted the enhanced efficacy of combined orthotic intervention and corticosteroid injections compared to individual modalities.[18,19] Unlike prior research, Suwannaphisit et al. suggested that ketorolac injection, a nonsteroidal anti-inflammatory drug, yielded superior functional outcomes and grip strength compared to steroid injection during a 6-week follow-up period among patients with DQT. [20] In addition to injectional treatments, earlier research has demonstrated the short-term effectiveness of physiotherapy regimens for patients with DQT.[18,21] In this study, implementing a physiotherapy program comprising manual massage, cryotherapy, and APL and EPB strengthening exercises may have yielded significant improvements in short-term functional outcomes across both study groups. Despite extensive comparisons between steroid injection and thumb-supported static hand-wrist splinting in existing literature, there has been no direct comparison between prolotherapy and steroid injection in DQT patients in the short-term follow-up. Our study aims to address this gap by elucidating the superior functional efficacy of steroid injection over prolotherapy in managing DQT.

Limitations: This study is subject to several limitations, the foremost being the absence of long-term follow-up, which restricts our ability to ascertain the sustained efficacy of the interventions

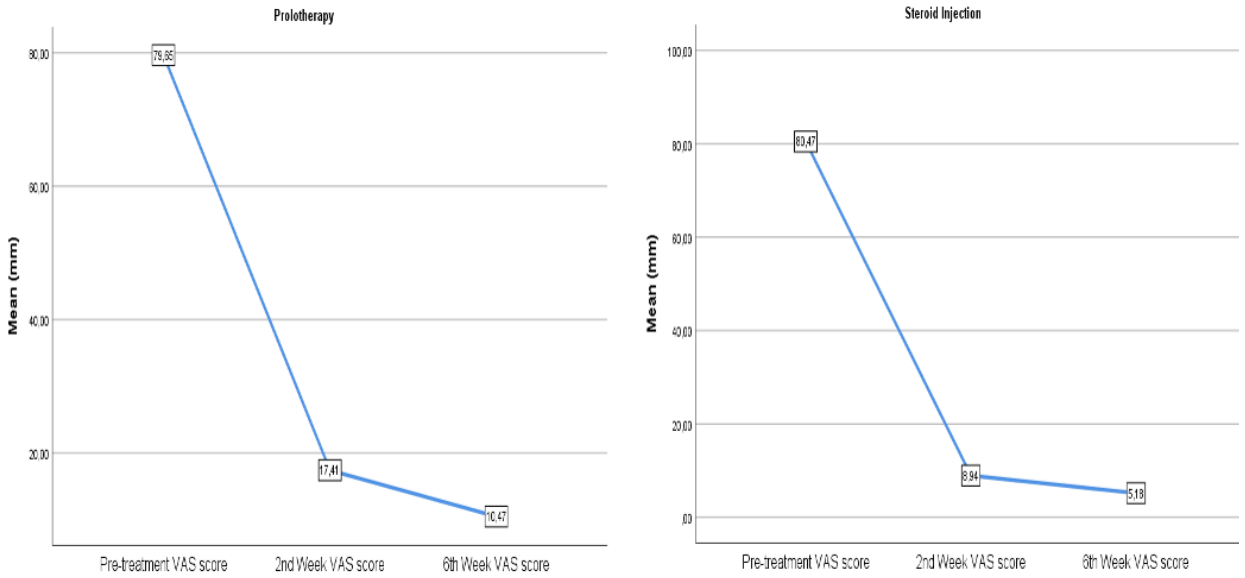

Figure 1. The alterations in VAS wrist pain scores over six weeks among groups.

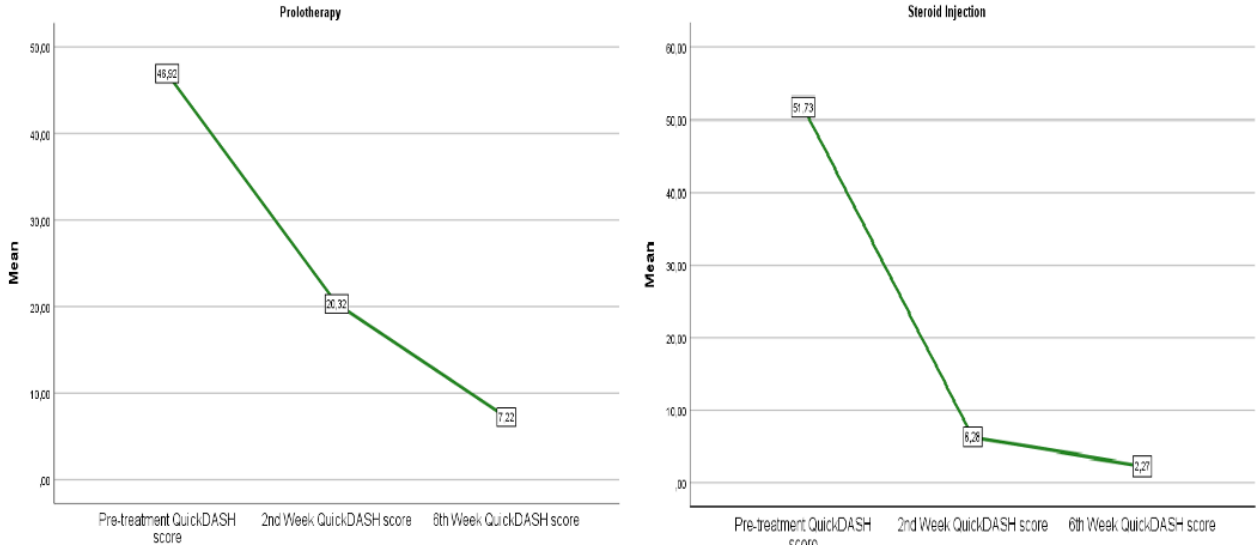

Figure 2. The alterations in QuickDASH function scores over six weeks among groups.

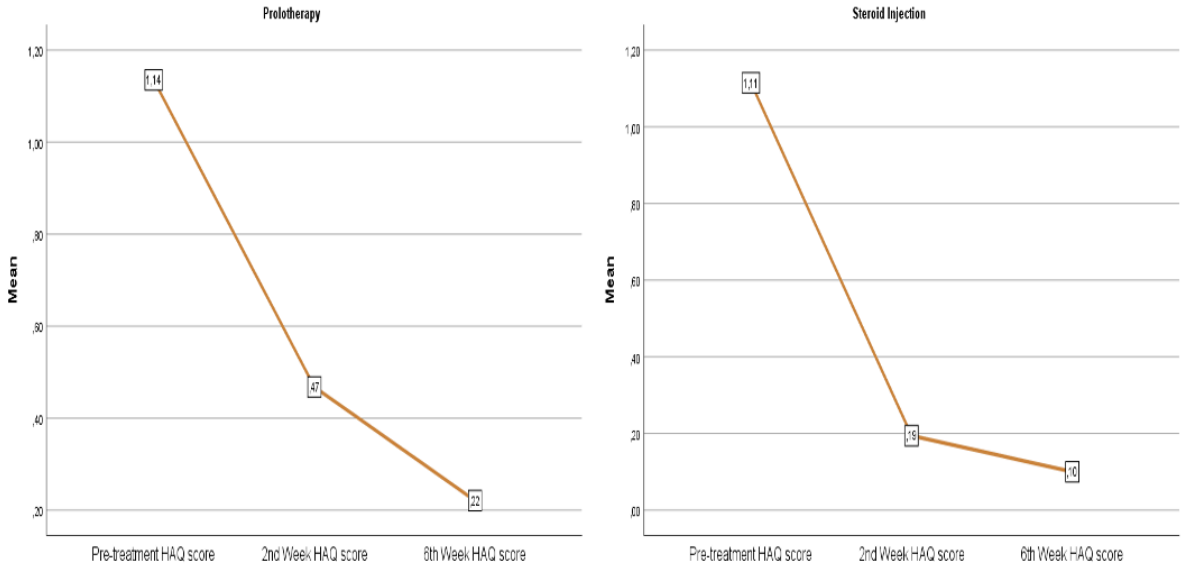

Figure 3. The alterations in HAQ function scores over six weeks among groups.

studied. Secondly, inadequate data collection regarding patient compliance with the prescribed home-based physiotherapy program, coupled with a lack of comprehensive exercise follow-up charts, limits our understanding of the potential impact of this adjunctive physiotherapy on treatment outcomes. These limitations emphasize the need for future research endeavours to incorporate extended follow-up periods and careful monitoring of patient adherence to prescribed physiotherapy protocols, thereby enhancing the robustness and applicability of study findings in clinical practice.

Conclusion

The results of this study shed light on the effectiveness of steroid injection versus prolotherapy in managing wrist pain and improving functional outcomes among DQT patients. Notably, the steroid injection group experienced greater improvements in wrist pain levels and functional abilities compared to the prolotherapy group, with these differences continued at the six-week follow-up. These results highlight the potential benefits of steroid injection over prolotherapy for patients suffering from DQT. The findings provide valuable insights to orthopedic practitioners, enabling them to make informed decisions regarding treatment options for their patients. Further research is necessary to explore the long-term outcomes and potential underlying mechanisms of these therapeutic effects on the prognosis of DQT.

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ORCID and Author contribution: All authors reviewed and approved the final manuscript. **H.Z. (0000-0002-5323-8245):** Conception, design of the study, interpretation of data, writing and drafting, and revision. **G.B. (0000-0001-9224-996X):** Conception, design of the study, literature search, statistical analysis, writing and drafting, and revision.

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RESEARCH ARTICLE

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The protective effect of venlafaxine on hydrogen peroxide-induced cytotoxicity in C6 glioma cells

Venlafaksi'nin C6 Glioma Hücrelerinde Hidrojen Peroksit Kaynaklı Sitotoksisitede Koruyucu Etkisi

Adem Ahlatcı[1], Kenan Yıldızhan[2*], Ahmet Şevki Taskıran[3]

1.Vocational School of Health Services, Van Yuzuncu Yil University, Van, Türkiye
2.Department of Biophysics, Faculty of Medicine, Van Yuzuncu Yil University, Van, Türkiye
3.Department of Physiology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye

ABSTRACT

Aim: Neurodegeneration is the progressive loss and structural deterioration of neuronal cells. Hydrogen peroxide (H_2O_2) is formed by dismutation and causes oxidative stress in neuronal cells. Venlafaxine is a drug that increases both serotonin and noradrenaline in the synaptic gap.In this study, the effect of venlafaxine on H2O2-induced cytotoxicity in C6 cells was investigated.
Methods: First of all, different doses of venlafaxine (25, 50, and 100 µM) were tried to find the appropriate dose in C6 glioma cells. Then, the effect of venlafaxine on H_2O_2-induced cytotoxicity in the cells was investigated. For this purpose, cell viability rate, proinflammatory markers IL-1β and TNF-α, and NO and iNOS levels were examined by ELISA kits.
Results: H_2O_2-treated caused cytotoxicity in the C6 glioma cells; when venlafaxine 25, 50, and 100 µM doses were evaluated in terms of cell viability, it was observed that the 100 µM venlafaxine applied group significantly increased cell viability compared to the other groups. When we look at the levels of IL-1β and TNF-α, it is observed that there is an increase in the H_2O_2 applied group and a significant decrease in the venlafaxine (100 µM) applied group. It was observed that NO and iNOS levels increased in the H_2O_2 applied group compared to the other groups. It was observed that Venlafaxine treatment reduced the increased NO and iNOS levels caused by H_2O_2.
Conclusion: The study results showed that venlafaxine may have a protective effect on H_2O_2-induced cytotoxicity in C6 glioma cells.

Key Words: Cytotoxicity, C6 cells, Venlafaxine, Hydrogen Peroxide

ÖZ

Amaç: Nörodejenerasyon, nöron hücrelerinin ilerleyici kaybı ve yapısal bozulmasıdır. Hidrojen peroksit (H_2O_2) dismutasyonla oluşur ve nöron hücrelerinde oksidatif strese neden olur. Venlafaksin, sinaptik boşlukta hem serotonini hem de noradrenalini artıran bir ilaçtır.Bu çalışmada venlafaksi'nin C6 hücrelerinde H_2O_2 kaynaklı sitotoksisite üzerindeki etkisini araştırıldı.
Yöntem: Öncelikle C6 glioma hücrelerinde uygun dozu bulmak için farklı dozlarda venlafaksin (25, 50 ve 100 µM) denendi. Daha sonra venlafaksi'nin hücrelerde H_2O_2 kaynaklı sitotoksisite üzerine etkisi araştırıldı. Bu amaçla hücre canlılık oranı, IL-1β, TNF-α, NO ve iNOS düzeyleri ELISA kitleri ile incelendi.
Bulgular: H_2O_2 ile inkübasyon C6 glioma hücrelerinde sitotoksisiteye neden oldu. Venlafaksin 25, 50 ve 100 µM dozları hücre canlılığı açısından değerlendirildiğinde, 100 µM venlafaksin uygulanan grubun diğer gruplara göre hücre canlılığını anlamlı düzeyde arttırdığı görüldü. IL-1β ve TNF-α düzeylerine bakıldığında H_2O_2 uygulanan grupta artış, venlafaksin (100 µM) uygulanan grupta ise IL-1β ve TNF-α düzeylerinde anlamlı oranda azalma olduğu görüldü. H_2O_2 uygulanan grupta NO ve iNOS düzeylerinin diğer gruplara göre arttığı gözlendi. Venlafaksin tedavisinin H_2O_2'nin neden olduğu artan NO ve iNOS düzeylerini azalttığı görüldü.
Sonuç: Çalışma sonuçları venlafaksinin C6 glioma hücrelerinde H_2O_2 kaynaklı sitotoksisite üzerinde koruyucu etkiye sahip olabileceğini gösterdi.

Anahtar Kelimeler: Sitotoksisite, C6 hücreleri, Venlafaksin, Hidrojen peroksit

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*Corresponding Author: Kenan YILDIZHAN, Ph.D. Department of Biophysics, Faculty of Medicine, Van Yuzuncu Yil University, TR- 65080, Van, Türkiye. Phone: +904322150471 / mail: kenanyldzhan@gmail.com

ORCID: 0000-0002-6585-4010

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Introduction

The development of neurodegenerative illnesses is significantly influenced by oxidative stress (OS). Compared to other organs, the brain is especially susceptible to OS [1]. Despite only accounting for 2% of the body's weight, the brain utilizes approximately 20% of the oxygen provided by our metabolism. This high oxygen consumption makes the brain more susceptible to oxidative stress than other organs. Neuron and glial cells, owing to their high metabolic activity, are particularly vulnerable to OS and mitochondrial dysfunction [2].

Venlafaxine is an antidepressant drug that increases both serotonin and noradrenaline in the synaptic cleft [3]. Venlafaxine is a medication that is used to treat various diseases such as attention deficit disorder, diabetic neuropathy, migraine prophylaxis, obsessive-compulsive disorder, fibromyalgia, post-traumatic stress disorder, and premenstrual dysphoric disorder [4]. It can be used alone or in combination with other drugs for these diseases. Although venlafaxine is as effective as tricyclic antidepressant group drugs, it has better tolerability and fewer side effects than this group of drugs [5].

One of the most commonly used chemicals in creating oxidative stress models in in vitro studies is hydrogen peroxide (H_2O_2) [6]. H_2O_2 is a molecule that acts as a signal inside and outside cells. It can influence the fate of cells. At low levels, it helps with cell growth, immunity, and metabolism. However, when cells are exposed to high levels of H_2O_2, which are not natural, it can cause oxidative stress. If stress is not relieved, the cell may go into apoptosis [7]. It is routine practice to study astrocyte function, including oxidative stress measures, using C6 glioma cells. Furthermore, these cells react fast to outside stimuli like H_2O_2, which might result in OS [8]. Sugammadex (SUG) was found to have an adverse effect on C6 glial cells' viability following H_2O_2-induced oxidative stress and apoptosis, according to a study by Sahin et al. This study also showed that SUG increased H_2O_2-induced damage and reduced C6 cell viability after H_2O_2-induced oxidative stress [9]. Although there are some studies about venlafaxine in the literature, the exact protective effect and basic mechanisms of Venlafaxine against oxidative damage in C6 glial cells are unclear. Therefore, we investigated in this work how well venlafaxine protected C6 glial cells from H_2O_2-induced oxidative damage and how this effect related to the levels of iNOS, TNF-α, IL-1β, nitric oxide (NO), and cell survival rate.

Materials and Methods

Cell line and chemicals

C6 cells were obtained from ATCC, and Venlafaxine and H_2O_2 (Sigma-Aldrich Co., St Louis, MO, USA) were dissolved in DMEM. Stock solutions were prepared before treatment.

Cell Viability Assays

The cells were grown in DMEM supplemented with 10% fetal bovine serum, 1% L-glutamine, and 1% penicillin/streptomycin (Sigma-Aldrich Co., St Louis, MO, USA). Cells were kept in a humidified environment with 5% CO_2 at 37 °C. The cells in a well-growing state were seeded on 96-well plates at a density of 1×10^4 cells per well, and venlafaxine and H_2O_2 were added according to the experimental group. The control group was not administered any medication. Cells in the H_2O_2 group were treated with 0.5 mM H_2O_2 for 24 hours [10]. Cells in the Venlafaxine group were treated with venlafaxine at different concentrations (25, 50, and 100 µM) for 24 h [11]. Cells in the Venlafaxine + H_2O_2 group were pretreated with venlafaxine for 1 h with different concentrations (25, 50, and 100 µM) and then exposed to 0.5 mM H_2O_2 for 24 h. The experiment measured cell viability between groups using the Cell Counting Kit-8 (CCK-8) assay. The BioTek ELx808™ instrument was used to measure cell viability at OD450 nm by following the instructions provided in the commercial kits. The data were presented as a percentage compared to the control group (% of control). After examining the cell viability rates, it was determined that a dose of 100 µM was appropriate for venlafaxine. The cells were multiplied again, and four groups were created: control, H_2O_2, venlafaxine+H_2O_2, and venlafaxine.

Measurement of Biochemical Parameters

The cells were lifted using 0.25% Trypsin-EDTA and placed into sterile falcon tubes when they

achieved 80% confluency. After that, the tubes were centrifuged for 20 minutes at 1000 rpm, following the directions on the commercial kits. To make a cell suspension, the cell pellets were suspended in PBS (pH 7.4) after the supernatants were removed. Repeated rounds of freezing and thawing were used to lyse the cells and release their internal components. Following a 10-minute centrifugation at 4000 rpm and 4°C, the mixture was collected, and the supernatants were collected for biochemical analysis. The total protein levels in the samples were ascertained using the Bradford protein assay kit (Merck Millipore, Darmstadt, Germany). IL-1β, TNF-α, NO, and iNOS levels were measured at OD450 nm using commercial ELISA kits and the BioTek ELx808TM device following the instructions provided in the kit procedure (YL Biont, Shanghai, China).

Statistical Analysis

The data was analyzed using SPSS software (Version 23.0) with one-way ANOVA. For any significant differences observed in the data, the post-hoc Tukey test was used. The level of statistical significance was set to $p < 0.05$. All data are expressed as mean ± standard deviation.

Results

Effect of venlafaxine on the cell viability exposed to H_2O_2

The cell viability for venlafaxine was determined in both control and glutamate-treated C6 cells at various doses (25, 50, and 100 µM/mL). The cells were pretreated with increasing doses of Venlafaxine for 1 h and then incubated with or without 0.5 mM H_2O_2 for the next 24 h. As seen in Figure 1, it was observed that the doses used only for Venlafaxine did not affect cell viability compared to the control group. It was determined that applying a dose of 100 µM/mL Venlafaxine to groups with H_2O_2 toxicity significantly increased the cell viability rate ($p < 0.05$). It was observed that cell viability decreased as the Venlafaxine dose decreased in the Venlafaxine+ H_2O_2 groups ($p < 0.05$).

Effect of venlafaxine on TNF-α and IL-1β levels in H_2O_2-induced cytotoxicity

As seen in Figure 2A, after the appropriate dose of Venlafaxine (100 µM/mL) was selected for treatment, TNF-α levels were measured after the specified incubations in the groups. Compared to the control group, the TNF-α level of the H_2O_2 group was significantly higher ($p < 0.05$). While the TNF-α level in the Venlafaxine+ H_2O_2 group was higher than in the control group, it was lower than in the H_2O_2 group ($p < 0.05$). There was no significant difference in TNF-α level in the Venlafaxine group compared to the control group, but it was lower compared to the Venlafaxine+ H_2O_2 and H_2O_2 groups ($p < 0.05$).

When the effect of venlafaxine against H_2O_2 cytotoxicity was measured with the IL-1β level Elisa kit in C6 cells, it was seen that the IL-1β level of the H_2O_2 group was at the highest level compared to all other groups ($p < 0.05$). It was determined that the IL-1β level in the Venlafaxine + H_2O_2 group was higher than the control group but lower than the H_2O_2 group ($p < 0.05$). There was no significant difference in IL-1β level in the Venlafaxine group compared to the control group ($p > 0.05$), but it was lower than the Venlafaxine+ H_2O_2 and H_2O_2 groups ($p < 0.05$) (Figure 2B).

Effect of venlafaxine on NO and iNOS level in H_2O_2 induced cytotoxicity

The H_2O_2 group had the highest NO and iNOS levels compared to all other groups ($p < 0.05$). There was no statistically significant difference between the control, venlafaxine, and venlafaxine+ H_2O_2 groups ($p > 0.05$). When the venlafaxine+ H_2O_2 group and the H_2O_2 group were compared between the groups, it was determined that NO and iNOS levels were significantly lower in the venlafaxine+H_2O_2 group ($p < 0.05$) (Figure 3A and B).

Discussion

OS occurs when there is an imbalance between oxidant substances in the body and antioxidant defence systems; one of the most prominent indicators is the increase of reactive oxygen species within the cell. As a result, reactive oxygen species overproduction causes damage to tissues and disrupts normal physiological functions. Studies have confirmed that oxidative stress is a factor in the onset and progression of neurodegenerative diseases in the central nervous

system [12, 13].

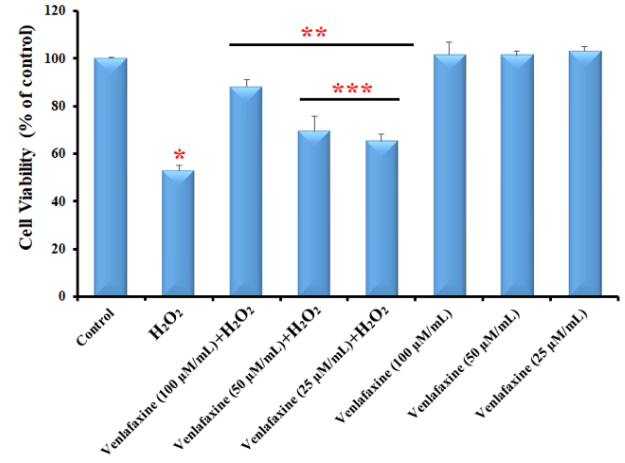

Figure 1. Effect of venlafaxine on cell viability in H_2O_2 induced cytotoxicity in C6 cells. All data are presented as the means ± SD. *p<0.05, compared with the control group; **p<0.05, compared with control and H_2O_2 groups, ***p<0.05, compared with Venlafaxine (100 µM/mL) + H_2O_2 group

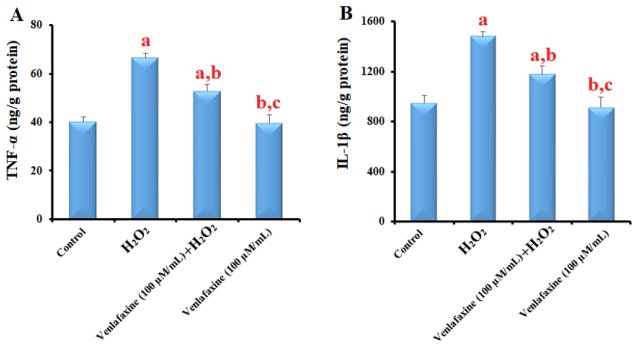

Figure 2. Effect of venlafaxine on TNF-α (A) and IL-1β (B) levels in H_2O_2 induced cytotoxicity in C6 cells. All data are presented as the means ± SD. ap<0.05, compared with the control group; bp<0.05, compared with H_2O_2 group, cp<0.05, compared with Venlafaxine (100 µM/mL) + H2O2 group.

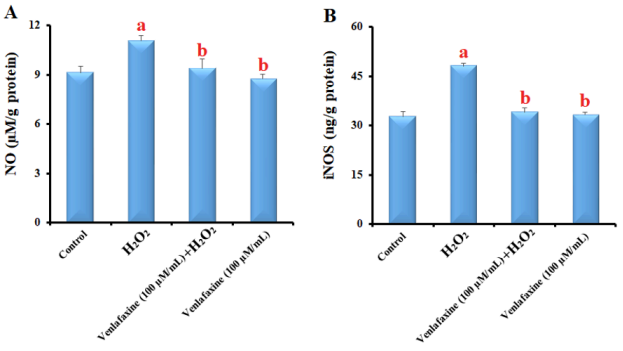

Figure 3. Effect of venlafaxine on NO (A) and iNOS (B) levels in H_2O_2 induced cytotoxicity in C6 cells. All data are presented as the means ± SD. ap<0.05, compared with the control group; bp<0.05, compared with H_2O_2 group.

Venlafaxine is primarily known for its antidepressant effects. However, recent studies have begun to unveil its potential neuroprotective properties. For instance, venlafaxine has been shown to protect against glutamate-induced cytotoxicity in PC12 cells, suggesting a broader neuroprotective role that could be attributed to its antioxidative properties [14]. Similarly, research by Eren et al. demonstrated that venlafaxine could mitigate depression-induced oxidative stress in the rat brain, further supporting the notion that venlafaxine possesses antioxidative and neuroprotective effects [15]. Cytotoxicity induced by H_2O_2 and the resulting increase in OS is considered one of the mechanisms underlying many pathological conditions, such as cell death, DNA damage, and inflammation. H_2O_2 increases oxidative stress by affecting intracellular signalling pathways, which can lead to dysfunction in various cell types [16]. This result is consistent with the study conducted by Abdel-Wahab et al. in 2011, suggesting the potential antioxidant properties of venlafaxine and its capacity to reduce oxidative damage [17]. In the current study, we observed that venlafaxine treatment significantly improved the viability of cells exposed to H_2O_2 (Figure 1).

TNF-α and IL-1β are cytokines that play a vital role in inflammation [18]. These cytokines act on various cellular functions such as cell death, cell proliferation, differentiation, and modulation of immune responses. The increase in TNF-α and IL-1β levels occurs due to multiple stimuli such as cellular stress, tissue damage, or pathogenic invasion. For example, cytotoxicity induced by ROS such as H_2O_2 can trigger the production of TNF-α and IL-1β by increasing intracellular oxidative stress and bypassing cellular defence mechanisms. Excessive production of these cytokines plays a central role in the pathophysiology of inflammation and may contribute to the progression of cellular damage and tissue dysfunction [19-21]. This study showed that the TNF-α level in the H_2O_2 group was significantly higher than the control group. TNF-α level in the venlafaxine+ H_2O_2 group is higher than the control group but lower than the H_2O_2 group. In the Venlafaxine group, the TNF-α level is similar to the control group and lower than the Venlafaxine+ H_2O_2 and H_2O_2 groups. Regarding IL-1β level, the H_2O_2 group has the highest value

compared to all other groups. The venlafaxine + H_2O_2 group had a higher IL-1β level than the control group but lower than the H_2O_2 group. The IL-1β level of the Venlafaxine group did not show a significant difference with the control group but was lower than the Venlafaxine+ H_2O_2 and H_2O_2 groups (Figure 2A and B).

Studies have shown that NO and iNOS are critical mediators in intracellular signalling pathways and inflammatory processes. In particular, high NO levels produced by iNOS are a source of nitrosative stress that can cause cell damage and death [22, 23]. The findings of this study, consistent with this literature, show that H_2O_2-induced oxidative stress is associated with an increase in NO and iNOS levels. The increase in NO and iNOS levels after H_2O_2 exposure may increase cellular damage through the synergistic effects of oxidative and nitrosative stress [24]. This may be important in understanding pathological processes such as neurodegenerative diseases and inflammation. For example, neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease have been associated with increased oxidative and nitrosative stress [25]. The current study showed that the H_2O_2 group had the highest NO and iNOS levels compared to all other groups. There was no statistically significant difference between the control, venlafaxine, and venlafaxine+ H_2O_2 groups. When the venlafaxine+ H_2O_2 and H_2O_2 groups were compared, it was determined that NO and iNOS levels were significantly lower in the venlafaxine+ H_2O_2 group (Figure 3A and B). These results suggest that venlafaxine may be a potential therapeutic agent in modulating cellular stress responses of NO and iNOS.

Conclusion

In this study, the effect of venlafaxine on viability, TNF-α, IL-1β, NO, and iNOS levels in C6 cells exposed to H_2O_2-induced cytotoxicity was investigated. The results indicate that venlafaxine can increase the viability of C6 cells under oxidative stress and modulate the inflammatory response.

Conflict of Interest: The authors declare that they have no conflicts of interest.

Ethics Declarations: The current study has no study with human and human participants. The study is not subject to ethics committee approval.

ORCID and Author contribution: A.A. (0000-0002-5109-2000), K.Y. (0000-0002-6585-4010), A.Ş.T. (0000-0002-5810-8415). All the authors designed the study, performed the experiments, and analyzed the data. AA performed biochemical parameters. KY drafted the manuscript. All authors read and approved the final manuscript.

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